(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 26 April 2001 (26.04.2001)

PCT

(10) International Publication Number WO~01/29221~A2

- (51) International Patent Classification⁷: C12N 15/12, 15/19, C07K 14/47, 14/705, 14/52, C12N 1/21, C07K 16/18, 16/24, 16/28, C12N 5/10
- (21) International Application Number: PCT/US00/29052
- (22) International Filing Date: 20 October 2000 (20.10.2000)
- (25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/160,712

20 October 1999 (20.10.1999) U

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

 Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.

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Description

NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

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shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEO ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 15 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides 20 encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a 25 DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computerreadable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

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Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment 5 that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, FlagTM peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide, 15 thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

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"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

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"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α -globin, β -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

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The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

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A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436. Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, *Nuc. Acids Res.* 14:4683, 1986) are not always exact and may vary by as much as \pm 5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

Table 1

<u>Protein</u>	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	. 82	21
AFP310695	84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	17
AFP356885	130	17
AFP226938	132	16
AFP138504	134	29
AFP359196	136	24
AFP501809	138	27
AFP152733	140	15
		23
AFP541394	142	
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	. 25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270	16
AFP275580	272	28
AFP298054	274	21
AFP348226	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19

AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	· 16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	25

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AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	- 16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27

A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	. 236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

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AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

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AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and anti-viral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., *J. Biol. Chem.* 227:5784-5789, 1996).

This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

5 Table 3

•	Table 3
Locus	Accession Number & Description
AFP130852	AE003823 (fly genomic)
AFP169968	AE003515 (fly genomic)
AFP174843	AF283518 (Mus musculus elongation factor sec)
AFP176427	AE003808 (fly genomic)
AFP178828	PSN_V61483
AFP179530	AE003708 (fly genomic)
AFP188135	AE003677 (fly genomic)
AFP195042	PIR_T41241 (yeast oxysterol-binding protein family)
AFP198645	AE003718 (fly genomic)
AFP199200	AF113691 (human clone FLB4739 PRO1238 mRNA)
AFP204736	AC069237 (human chromosome 3 clone RP11-175M9)
AFP229269	AF247177 (Mus musculus sphingosine-1-phosphate
	phosphohydrolase)
AFP230872	AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AFP279267	AE003559 (fly genomic)
AFP347179	AE003499 (fly genomic) Z1041035F6P
AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP359196	AE003530 (fly genomic)
AFP374312	AE003538 (fly genomic)
AFP389687	AE003831 (fly genomic)
AFP395942	AB041564 (mouse brain cDNA; clone MNCb-0914)
AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP477303	AE003778 (fly genomic)
AFP62060	PSP_Y94938 (Human secreted protein clone ye78_1)
AFP71288	AL161655 (human chromosome 20 clone RP11-116E13)
AFP74517	PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology:
	molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by
	BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone:RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

Locus	Accession Number & Description	
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)	
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)	
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)	
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close	
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)	
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)	
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)	
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology	
	to PSP_W35393 Human TB2 gene product)	
AFP202885	AB037808 (human mRNA for KIAA1387 protein)	
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)	
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)	
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)	
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak	
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)	
AFP250422	AF208849 (human BM-007 mRNA)	
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to	
	major facilitator protein homolog, fission yeast: PIR_S62432)	
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)	
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak	
	homology to dinitrogenase reductase activating glycohydrolase (draG)	
	Archaeoglobus fulgidus: PIR_C69465)	
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on	
	chromosome 10. Contains a novel gene and the 5' end of the gene for a	
	novel protein; ortholog of mouse FISH protein)	
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)	
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)	
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)	
AFP324816	, , , , , , , , , , , , , , , , , , , ,	
	Human O-linked GlcNAc transferase mRNA)	

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)		
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to		
	human bisphosphate 3'-nucleotidase mRNA: AF125042)		
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely		
	human orthologue of Rattus norvegicus small rec (srec) mRNA:		
	AF228917)		
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)		
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)		

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584, Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to $E.\ coli\ \beta$ -galactosidase (1,021 residues; see Casadaban et al., $J.\ Bacteriol.\ 143:971-980,\ 1980)$, a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

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are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

	Nucleotide	Resolutions	Complement	Resolutions
-	A	A	Т	T
	C	C .	G	G
	G	G	С	C
	T	T	Α	Α
	R	A G	Y	C T
	Y	C T	R	A G
	M	A C	K	G T
	K	G T	M	A C
	S	C G	S	C G
	W	A T	W	A T
	H	A C T	D	A G T
	В	C G T	V	A C G
	V	A C G	В	C G T
	D	A G T	Н	A C T
	N	A C G T	N	A C G T

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter	* .	Degenerate
Acid	Code	Codons	Codon
Cys	С	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	Α	GCA GCC GCG GCT	GCN
Gly	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	H	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	$\mathbf{F}_{\mathbf{r}}$	TTC TTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	•	TAA TAG TGA	TRR
Asn Asp	В		RAY
Glu Gln	Z		SAR
Any	X		NNN
Gap	-		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

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exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying 5 Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

Table 8

K562 cells
T-cells
testis
fetal liver or spleen
fetal liver or spleen
testis
placenta
fetal liver or spleen
adult brain
epidermal breast keratinocytes
breast
infant brain
testis
testis
fetal heart
K562 cells
testis
infant brain
germinal center B-cells
kidney
neonatal keratinocytes
peripheral blood eosinophils of asthma patients
K562 cells
fetal liver or spleen
testis
pregnant uterus
germinal center B-cells
fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex TaqTM; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or AdvantageTM 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

- 1 1	5 6 7 8 9 10		Table 9	13	41	15	16 17	18	19 20	21	22
	y	+	y	×	, , ,	+	,	1	+	╁╌	n
y y y	y y y y	E	у	у	y		n y	у	n y	п	n
y y y	y y y y	χ	У	у	'n	y y	, y	у	y y	u	y
у у у	y y y y	y	y	y	λ	уу	γ ,	>	уу	u	у
у у у	y y 'y y	λ	У	y	'n	y	, y	у	y y	n	n
y y y	y y y y	у	У	У	у	y	, y	y	y y	u	y.
y y	y y y y	y	У	y	y	y	, y	y	y	п	>-
y y y	y y y	ш	y	y	y	y y	, y	y	уу	п	y
y y y	y y y	y	у	У	y	y	/ y	y	y y	u	ш
y y y	y y n y	y	у	У	γ	y y	/ { y	y	уу	ш	>
y y y	y y y y	y	У	У	y	y }	у ју	y	y y	п	>
n n	n n n	п	n	n	u	n r	u u	u	n n	и	u
y n n	n n n	_	n	n	u	u u	u ı	u	uu	u	u
y y y	y y y y	y	у	ý	у	y	, y	ý	уу	u	>
y y y	y y y	y	у	u	y	y		>	y	п	>
y y y	y n n y	ď	n	n	y	u u	ı n	y)	y y	. u	у
y y y	y y y y	y	y	λ	y	y y	, y	y	уу	u	>
y y y	y y y	y	у	У	y	yyy	/ J	l y	y y	n	u .
n n y	y y n n	п	u	n	u	y	n n	u	u u	n	y
y y y	y	у	У	у	y	y y	, y	у	y y	u	()
y y y	y y y y	У	>	y	у	y y	, y	y	yy	u	y
y y y	y y y y	y	, V	у	y	y y		y	y y	u	у
y y y	y n y y	λ	y	У	y	y y	u /	у	уу	u	y
y y y	y y y y	р	y	у	y	y y	u /	у	y y	u	u
y y y	y y n y	у	у	n	y	y y	/ y	y	yy	u	c
y y y	y y y y	y	У	y	y	yyy	γ ,	y	y y	u	у
y y y	y y y y	y	у	y	×	уу	, y	y	y	E .	Δ
y y y	y y y y	y	y	у	ý	y (y	, y	~	y	u	>
y y y	y y y y	ý	y	п	>	y	, x	^	y	п	
y y y	y y y y	u	у	y	pu		nd nd	>	y	п	\frac{1}{2}
y y y	y y y y	y	y	y	λ	y	, y	'n	y	п	Y
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	10 11 12 13 14 15 16 17 18 19 20 21	n y y y y y y y y y y y	y y y y y y y y y y y y y	y y y y y y y y y y n	y h d y y y y y y y y y y y y	y y n y y y y	y y y y y y y y y y n	u u u u u u u u u u u		y y y y y y y y y	y y y y y y y y y y y n	y y n y n y y y	A A A Pu A A A A A A	y y y y y y y y y y n	n n n n y n n n	y. y y y y y nd y y y n	y y y y y y y y y y y	y y y y y y y y y y y y y	y y y y y y y y y y y	u v bu v v v v bu v v u v		^ ^ ^ ^ ^ ^ ^ ^ ^ ^
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	6	>	^	>	멸	>	z.	c		ı.	y	>	'n	=	E .	y	V	>	×	>	c	>
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	9	>	×	>	×	>	y	u	u	y	у	Y	<u>~</u>	×	y	y	y	y	y	^	_	>
	2	Y	y	>	λ	>	y	n	п	у	Y	u	y	y	u	y	У	y	y	>	=	>
i	4	y	y	y	у	y	У	y	u	y	y	У	y	j y	u	у	y	y	У	~	=	^
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ntinue	1	y	у	y	У	У	>	=	ш	Y	γ	y	χ	y	λ	y	y	у	y	у	u	>
Table 9, continued	Protein	AFP324816	AFP325761	AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517

peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H₂O; 22, genomic DNA. Y=yes; n=no; nd=not determined.

Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

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The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

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Probes and primers as disclosed herein can be used for cloning allelic. orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable), digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells 15 include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb. Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 20 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

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Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning et al., *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (e.g., Sf9 or Sf21 cells) or *Trichoplusia ni* (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10⁵ cells to a density of 1-2 x 10⁶ cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, *ibid.*; O'Reilly et al., *ibid.*; Richardson, *ibid.*). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

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Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (*Bangalore*) 11:47-58, 1987.

Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

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Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

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Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, *Chem. Pept. Prot.* 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

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Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the CytosensorTM Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., *Investigational New Drugs* 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, *Methods Enzymol.* 109:749-773, 1985; Wahl et al., *Mol. Cell Biol.* 8:5016-5025, 1988; and Cook et al., *Analytical Biochem.* 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., *J. Immunol. Methods* 82:169-179, 1985), and use of tetrazolium salts (Mosmann, *J. Immunol. Methods* 65:55-63, 1983; Alley et al., *Cancer Res.* 48:589-601, 1988; Marshall et al., *Growth Reg.* 5:69-84, 1995; and Scudiero et al., *Cancer Res.* 48:4827-

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4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO₂ atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. ³H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, *J. Immunol. Methods* 120:271-276, 1989; Greenfeder et al., *J. Biol. Chem.* 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as ³H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, *ibid.*).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using ³H-proline incorporation into nascent secreted collagen.

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SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1 β and TNF α levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (*J. Biol. Chem.* 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately $10^4 - 10^5$ cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

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246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. <u>183</u>:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 α or IL-1 β is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g., γ counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol*: 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol*. 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACoreTM, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

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Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

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chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant K_i is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin (Steiner et al., <u>J. Biol. Chem. 267</u>:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. <u>270</u>:25411-25417, 1995).

Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., *J. Biol. Chem.* 263:14621-14624, 1988; Wu et al., *J. Biol. Chem.* 267:963-967, 1992; and Johnston and Tang, *Meth. Cell Biol.* 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition *in vivo*. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, *Brit. J. Dermatol.*

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118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB₄ levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO₂/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

35 Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine*

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., *Arch. Surg.* 128:423-429, 1993). A test substance is injected subcutaneiously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, *Advan. Enzyme Regul.* 35:293-301, 1995; Conway et al., *Clin. Exp. Metastasis* 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, *Semin. Thromb. Hemost.* 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* <u>81</u>:3998-4002, 1984.

Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

Table 10 Protein Hexapeptide N-termini AFP210015 AFP170681 AFP413680 AFP483037 AFP230872 AFP178828 AFP200134 AFP195796

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	[284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	[,] 86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	592	591	374	525
AFP75785	128	127	136	99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	118	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588 AFP176427 AFP192633 AFP193013 AFP193881 AFP195562 AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269 AFP232213					
AFP192633 AFP193013 AFP193881 AFP195562 AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	43	42	2	41	1
AFP193013 AFP193881 AFP195562 AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	311	290	308	155	288
AFP193881 AFP195562 AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	58	56	162	349	44
AFP195562 AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	47	90	87	46	68
AFP199922 AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	274	295	402	273	292
AFP204736 AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	274	295	339	473	273
AFP206179 AFP221877 AFP222758 AFP227032 AFP229269	57	55	74	180	50
AFP221877 AFP222758 AFP227032 AFP229269	89	58	43	28	23
AFP222758 AFP227032 AFP229269	74	80	73	71	70
AFP227032 AFP229269	32	31	30	50	75
AFP229269	44	43	75	42	19
	47	55	46	65	54
AFP232213	147	127	146	63	60
	44	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')₂ and Fab fragments, single chain antibodies, and the like, including genetically engineered antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include *in vitro* exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

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Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K_a) of 10^6 M^{-1} or greater, preferably 10^7 M^{-1} or greater, more preferably 10^8 M^{-1} or greater, and most preferably 10^9 M^{-1} or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, *Ann. NY Acad. Sci.* <u>51</u>: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity *in vitro* and *in vivo*.

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The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, Pseudomonas exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., ibid., ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, **OMIM**TM the Database, Johns **Hopkins** University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

			Table 11			
	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
	RP11-594B10	*	18	18q12	35729370	35952786
	RP11-691N7	*	Ξ	11p11.11	53438038	53888802
	RP11-79j21	AW580814	15	15q22.1	58185489	58481462
	3 £	AW580814	15		58258653	58308652
	RP4-591C20	*	20	20q12	48950838	49160243
	CTD-2289B16;RP11- 116N21;RP11-7F17	*	1 4	14q23.3	62132030	62313415
	CTC-539A10	*	12	12q12	41234876	41456630
		*	6	9q31.2	91150313	91361876
	RP11-901L	*	16	16q22.1	71944378	72167142
	RP11-31110	*	16	16q11.2	44574019	44904017
	BAC-R-1070N10	*	14		82330266	82541053
	BAC-R-804M7	*	14	14q21.3	46135365	46299284
	CTD-2521M24	*	19	19p13.3	4839920	5087628
	*	*	4	4p16.3	4521455	4544888
*		AI494556;AW85055 3	3	3q13.12	116466893	116517043
	RP11-541H12	*	_	1q22-23.3	161893354	162136704
\sim	RP11-312P12	*	10	10q22.1	81289799	81650062
	hRPK.264_B_14	*	17	17q23.3	64245127	64365313
		*	3	3q21.3	141329005	141513510
	RP11-707M3	*	8	8q13.3	75395740	75583383
		AI566086	10	10q11.1	52859924	52861338
	RP11-541N10	*	10	10q24.32	115276306	115467187
		AA421069	15	15q15.3	48427462	48427830
	RP11-532F12	*	15	15p11.1	17263661	17480097
		W52728	11	11q11	57918740	57927327
	2366B9	AW118928	9	6p22.3	19812023	19812791
	NH0469M07	*	2	2q33.1	205320800	205511307
H-4	RP11-15I20	*	2	2p21	49054619	49249783
	RP11-5024	*	2	2p24.3	17554756	17765537

		.1.					_	_	_	_	_			_				_			_
44786504	126134140	120124140	138/03140	128134389	3300034	4777403	143641730	1514256	59940397	19003942	173547400	70471703	16577531	50564907	60714738	700707001	100/24700	137478427	*	77633569	10000011
44087441	125018900	120667600	130001322	3470000	1100155	4109133	142961410	1512179	59897688	18993217	173540737	70222075	16401516	50554924	60450247	100404502	100424303	137477811	*	77419530	22221
17021 2	12024 23	1012 21 2	11,002 2	11425.3	16512.2	10p13.3		4p16.3	19q13.33	8p21.3	5033.1	16022 1	19n13 13	6n21.1	13021 1	13034	10h01	6477.33	1p35.1-36.13	4a21.22	
17	2	-	1=	1 2	16	2 .		4	19	∞	5	16	01	9	13	13	}	٥	1	4	
*	*	*	A1253088	AI741157	*	A11222777	A1133727	AI341602	*	AI814257	AI140615	*	*	AW583171	*	*	A A 400500C	AA493300	*	*	
CTD-2534121	*	3.28E+21	*	*	*	*	÷	*	cosmid-R31181	*	*	RP11-502K10	CTB-5E10	*	RP11-342J4	RP11-391H12	*		RP5-1056L3	RP11-791G16	
AC015936	AC025740	AL022240	*	*	AC004235	*	9	*	AC006942	*	*	AC009131	AC008686	*	AL138695	AL136221	*		HS1056L3	AC067942	
AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	ATCAOAGTA	AFF404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	2021	AFP/4517	AFP93743	
	AC015936 CTD-2534121 * 17021 2 44087441	AC015936 CTD-2534[2] * 17 17q21.2 4408744 AC025740 * 135918000	AC015936 CTD-2534[2] * 17 1742 .2 4408744 AC025740 * 12 1242.3 125918909 AL022240 3.28E+2 * 1 1,1,2,1,2 1,26,57550	AC015936 CTD-2534[2] * 17 17q21.2 44087441 AC025740 * 12 12q24.23 125918909 AL022240 3.28E+21 * 41753088 11 11,023.2	AC015936 CTD-2534[2] * 17 17g1.2 44087441 AC025740 * 12 12q24.23 125918909 AL022240 3.28E+21 * 1 1q12-21.2 138667522 * * AI253088 11 11q23.3 128134250 * * A7741157 16 16413.3 2470000	AC015936 CTD-2534I21 * 17 17q1.2 44087441 AC025740 * 12 12q24.23 125918909 AL022240 3.28E+21 * 1 1q12-21.2 138667522 * * AI253088 11 11q23.3 128134250 * * AI741157 16 16p13.3 3479999 AC004235 * * * 16 16p13.3 4190155	AC015936 CTD-2534I21 * 17 1741.1 13753433 AC025740 * 17 17421.2 44087441 AL022240 3.28E+21 * 1 1412-21.2 138667522 * * AL253088 11 11q23.3 128134250 * * AT741157 16 16p13.3 3479999 * * * * 4189155 *	AC015936 CTD-2534[2] * 17 1741.1 17533453 AC025740 * * 12 1242.23 125918909 AL022240 3.28E+21 * 1 1412-21.2 138667522 * * AI253088 11 11q23.3 128134250 * * AT741157 16 16p13.3 3479999 * * AI133727 7 142961410	AC0015936 CTD-2534[2] * 17 1741.1 1752342 AC025740 * 12 1242.23 125918909 * * 1 1402.21.2 138667522 * * AI253088 11 11q2-21.2 138667522 * * AI741157 16 16p13.3 3479999 AC004235 * AI133727 7 142961410 * * AI341602 4 4p16.3 1512179	AC015936 CTD-2534[2] * 17 1741.1 17923493 AC025740 * 12 17421.2 44087441 * AL022240 3.28E+21 * 1 1412-21.2 138667522 * * AL253088 11 11q23.3 128134250 * * AT741157 16 16p13.3 3479999 AC004235 * AT133727 7 4p163.3 1489155 * * AT133727 7 4p16.3 1512179 AC006942 cosmid-R31181 * 19 19q13.3 59897688	AC005936 CTD-2534[2] * * * * * * * * * * * * * * * * * * *	AC005936 CTD-2534[2] * 17 1741.1 17953493 AC025740 * 12 1241.2 44087441 * 4L022240 \$.28E+21 * 1 1412-21.2 138667522 * AL022240 \$.28E+21 * 1 1412-21.2 138667522 * AC004235 * AL741157 16 16p13.3 3479999 AC004235 * AL133727 7 4p16.3.3 1521179 * * AL341602 4 4p16.3 1512179 * * AL814257 8 8p21.3 173540737 * * AL140615 5 5633.1 173540737	AC005936 CTD-2534[2] * * * * * * * * * * * * * * * * * * *	AC015936 CTD-2534[21] * 17 17p1 13503432 AC025740 * 17 17q21.2 44087441 AL022240 3.28E+21 * 12q24.23 125918909 * * AI253088 11 1q12-21.2 138667522 * * AI741157 16 16p13.3 128134250 * * AI741157 16 16p13.3 4189155 * * AI141602 4 4p16.3 1512179 * * AI341602 4 4p16.3 15421779 * * AI440615 5 5q33.1 17022075 AC009131 RPI1-502K10 *	AC015936 CTD-2534[21] * 17 17p1 12p1 12p	AC015936 CTD-2534[21] * 17 17p1 12p1 12p	AC015936 CTD-2534[21] * 17 17p1 17p1 17p1 17p1 17p1 17p1 13p1 13p1 13p1 14087441 44087441 AC025740 * * 1 142 12s1918909 1 14021 14087421 12s1918909 1 1402224 12s134550 1 12s134550 1 12s134550 1 14c1 14c1	AC015936 CTD-2534[21] ************************************	AC015936 CTD-2534[21] * 17 1721.2 44087441 AC025740 * 12 1242.23 125918909 AL022240 * 12 1242.21.2 138667522 * * AI741157 16 1612.3.3 128134250 * * AI741157 16 16p13.3 3479999 AC004235 * AI741157 16 16p13.3 3479999 * * AI14157 16 16p13.3 3479999 * * AI14157 16 16p13.3 3479999 * * AI14157 16 16p13.3 3479999 * * AI141602 4 4p16.3 1512179 * * AI140615 5 5q33.1 173540737 * * AI140615 5 5q33.1 173540737 * * AC008686 CTB-5E10 * AW583171 6 6p22.1 70222075	AC015936 CTD-2534[21] **** 17 17p11 17p11 17p11 17p12 44087441 AC025740 * * 1 12q24.23 125918909 * * * 41253088 11 1q12-21.2 138667522 * * * AI741157 16 16p13.3 128134250 * * * AI741157 16 16p13.3 128134250 * * * AI741157 16 16p13.3 128134250 * * * AI133727 7 4p16.3 1489155 * * * AI341602 4 4p16.3 1512179 * * * AI341602 4 4p16.3 1512179 * * * AI340615 5 5q33.1 173540737 * * * AI140615 5 5q33.1 173540737 * * AL138695 RP11-	AC015936 CTD-2534121 *** 17 17q21.2 44087441 AC025740 * * 12 12q24.23 125918909 AL022240 3.28E+21 * 1 1q12-21.2 138667522 * AL022240 3.28E+21 * 1 1q12-21.2 138667522 * AL022240 3.28E+21 * AL741157 16 16p13.3 128134250 * AC004235 * AL741157 16 16p13.3 3479999 * AC004235 * AL133727 7 142961410 * AC006942 * AL1341602 4 4p16.3 142961410 * * AL341602 4 4p16.3 1512179 * * AL1340615 5 5q33.1 173540737 * * AL136521 AV583171 6 6p21.1 50554924 * * AC00866 CTB-5B11.3 * AA493506 6 <

If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

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(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

The bioactive conjugates described herein can be delivered intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDrawTM (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds, x-ray crystallography to determine the three-dimensional structure in atomic detail, nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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EXAMPLES

Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His₆ tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique SmaI site just downstream of the MBP-His₆-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of SmaI-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura⁺ transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (ibid.). 100-ml cultures in minimal glucose media containing casamino acids and 100 µg/ml ampicillin are grown at 37°C in 500-ml baffled flasks to $OD_{600} \approx 0.5$. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at -70°C.

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Example 3

For larger-scale protein preparation, 500-ml cultures of E. coli BL21 expressing the AFP-MBP-His6 fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH₂PO₄, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 µg/ml Leupeptin, 2 µg/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM 30 NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 μl 1 M NaCl and 250 μl of absolute ethanol. The plasmid pZMP6, which has been cut with SmaI, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (*S. cerevisiae*) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H₂O]) and incubated at 30°C. After about 48 hours, the Ura⁺ yeast

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transformants from a single plate are resuspended in 1 ml $_{2}$ O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 μ l acidwashed glass beads and 200 μ l phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 μ l ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 μ l $_{2}$ O.

Transformation of electrocompetent *E. coli* host cells (Electromax DH10BTM cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% BactoTM Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% BactoTM Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO₂, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine scrum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (LipofectamineTM Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

mixed with 605 µl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 µM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEQ ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:
 - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
 - a transcription terminator.
- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- 14. A method of producing a polypeptide comprising culturing the cell of claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
 - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

a transcription promoter;

- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

SEQUENCE LISTING

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-					gtg Val					-	-	-			336
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					agg Arg 135		-	-						-	432
	-				agc Ser	_	_	-	_	_		-			480
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					gtt Val		•	•	-		-		-		768

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	gtc Val															864
	gtg Val 290															912
	act Thr			_	-		_	-			_					960
-	gag Glu															1008
	cca Pro															1056
	tac Tyr															1104
	gga Gly 370															1152
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	atg Met															1248
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Thr 65	Arg	Thr	Ala	Phe	Ile 70	His	His	Arg	G1u	G1n 75	Val	Trp	Lys	Arg	Cys 80
Ile	Asn	Ile	Trp	Arg 85	Asp	Val	Gly	Leu	Phe 90	Gly	Val	Leu	Asn	G1u 95	Ile
Ala	Asn	Ser	Glu 100	Glu	Glu	Val	Phe	Glu 105	Trp	Val	Lys	Thr	Ala 110	Ser	Gly
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Gln 145	Val	Thr	Asn	Trp	Ser 150	Ser	Cys	Cys	Leu	Arg 155	Val	Phe	Ala	Trp	His 160
Pro	His	Thr	Asn	Lys 165	Phe	Αl̄a	Val	Ala	Leu 170	Leu	Asp	Asp		Val 175	Arg
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Leu	Ala 210	Val	Ala	Cys	Gln	Ser 215	Cys	He	Leu	Пe	Trp 220	Thr	Leu	Asp	Pro
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Ile	Tyr	Ser 355	Leu	Ser	Phe	Pro	G1u 360	Arg	Cys	Gly	Glu	G1y 365	Lys	Gly	Cys
Val	Gly 370		Ala	Lys	Ser	A1a 375		Ile	Val	Ala	Asp 380	Leu	Ser	Glu	Thr

Thr 385	Пе	Gln	Thr	Pro	Asp 390	Gly	G1u	Glu	Arg	Leu 395	Gly	Gly	Glu	Ala	His 400		
Ser	Met	Val	Trp	Asp 405	Pro	Ser	Gly	Glu	Arg 410	Leu	Ala	Val	Leu	Met 415	Lys		
Gly	Lys	Pro	Arg 420	Val	Gln	Asp	Gly	Lys 425	Pro	Val	Ile	Leu	Leu 430	Phe	Arg		
Thr	Arg	Asn 435	Ser	Pro	۷a٦	Phe	G1u- 440	Leu	Leu	Pro	Cys	G1y 445	Ile	Ile	G1n		
Gly	Glu 450	Pro	Gly	Ala	Gln	Pro 455	Gln	Leu	Ile	Thr	Phe 460	His	Pro	Ser	Phe		
Asn 465	Lys	Gly	Ala	Leu	Leu 470	Ser	Val	Gly	Trp	Ser 475	Thr	Gly	Arg	Ile	Ala 480	,	
His	He	Pro	Leu	Tyr 485	Phe	Val	Asn	Ala	G1n 490	Phe	Pro	Arg	Phe	Ser 495	Pro		
Val	Leu	Gly	Arg 500	Ala	Gln	Glu	Pro	Pro 505	Ala	Gly	Gly	Gly	Gly 510	Ser	Ile		
		515					520					525		Pro			
Asp	Pro 530	Leu	Pro	Gly	Pro	Pro 535	Pro	Val	Leu	Pro	His 540	Ser	Pro	His	Ser		
His 545	Leu														٠		
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		-	-		-					-	cgt Arg		144
											tat Tyr		192
											aat Asn		240
											gaa Glu 95		288
_	-						-				agt Ser		336
											gtt Val		384
											gat Asp		432
_			-			-				 	ngg Xaa		480
_		_	_			_	_				gga Gly 175		528
_	_		_	-	-			_	 -		ccc Pro		576
											cat His		624

								ccc Pro					672
								gtg Val					720
								atg Met					768
		-	-		-			ctt Leu 265					816
	-		_				_	gaa Glu					864
_			•	-		-	-	tca Ser		 -	 	_	 912
	_					_	-	tat Tyr	_				960
	-			-			_	ctc Leu					1008
_								gca Ala 345					1056
								ctt Leu					1104
								ctt Leu					1152

1200 ccc cag aca aat gag tgg acc cag gtt gct cca ctg tgc cta gga aga Pro Gln Thr Asn Glu Trp Thr Gln Val Ala Pro Leu Cys Leu Gly Arg 395 385 1233 gct gga gct tgt gtt gtg act gta aaa tta taa Ala Gly Ala Cys Val Val Thr Val Lys Leu * 410 405 <210> 4 <211> 410 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(410) <223> Xaa = Any Amino Acid <400> 4 Met Glu His Phe Met Glu Val Ile Arg Asn Gln Glu Phe Val Leu Leu Pro Ala Ser Glu Ile Ala Lys Leu Leu Ala Ser Asp Asp Met Asn Ile 25 Pro Asn Glu Glu Thr Ile Leu Asn Ala Leu Leu Thr Trp Val Arg His Asp Leu Glu Gln Arg Arg Lys Asp Leu Ser Lys Leu Leu Ala Tyr Ile 60 Arg Leu Pro Leu Leu Ala Pro Gln Phe Leu Ala Asp Met Glu Asn Asn 75 70 Val Leu Phe Arg Asp Asp Ile Glu Cys Gln Lys Leu Ile Met Glu Ala Met Lys Tyr His Leu Leu Pro Glu Arg Arg Pro Met Leu Gln Ser Pro 105 Arg Thr Lys Pro Arg Lys Ser Thr Val Gly Thr Leu Phe Ala Val Gly 120 Gly Met Asp Ser Thr Lys Gly Ala Thr Ser Ile Glu Lys Tyr Asp Leu 135 140 Arg Thr Asn Met Trp Thr Pro Val Ala Asn Met Asn Gly Arg Xaa Leu 150 155 Gln Phe Gly Val Ala Val Leu Asp Asp Lys Leu Tyr Val Val Gly Gly 165 170 Arg Asp Gly Leu Lys Thr Leu Asn Thr Val Glu Cys Tyr Asn Pro Lys

			180					185					190				
Thr	Lys	Thr 195		Ser	Val	Met	Pro 200		Met	Ser	Thr	His 205		His	Gly		
Leu	Gly 210		Ala	Val	Leu	Glu 215		Pro	Met	Tyr	Ala 220	Val	Gly	Gly	His		
Asp 225	Gly	Trp	Ser	Tyr	Leu 230	Asn	Thr	Val	Glu	Arg 235	Trp	Asp	Pro	Gln	A1a 240		
Arg	Gln	Trp	Asn	Phe 245	Val	Ala	Thr	Met	Ser 250	Thr	Pro	Arg	Ser	Thr 255	Val		
Gly	Val	Ala	Val 260	Leu	Ser	Gly	Lys	Leu 265	Tyr	Ala	Val	Gly	Gly 270	Arg	Asp		
Gly	Ser	Ser 275	Cys	Leu	Lys	Ser	Val 280	Glu	Cys	Phe	Asp	Pro 285	His	Thr	Asn		
Lys	Trp 290	Thr	Leu	Cys	Ala	G1n 295	Met	Ser	Lys	Arg	Arg 300	Gly	Gly	Val	Gly	,	
Va1 305	Thr	Thr	Trp	Asn	Gly 310	Leu	Leu	Tyr	Ala	Ile 315	Gly	Gly	His	Asp	Ala 320		
Pro	Ala	Ser	Asn	Leu 325	Thr	Ser	Arg	Leu	Ser 330	Asp	Cys	۷a٦	Glu	Arg 335	Tyr		
Asp	Pro	Lys	Thr 340	Asp	Met	Trp	Thr	A1a 345	Val	Ala	Ser	Met	Ser 350	Ile	Ser		
Arg	Asp	A1 a 355	Val	Gly	Val	Cys	Leu 360	Leu	Gly	Asp	Lys	Leu 365	Tyr	Ala	Val		
G1y	Gly 370	Tyr	Asp	Gly	Gln	A1a 375	Tyr	Leu	Asn	Thr	Va1 380	Glu	Ala	Tyr	Asp		
Pro 385	Gln	Thr	Asn	G1u	Trp 390	Thr	Gln	Val	Ala	Pro 395	Leu	Cys	Leu	Gly	Arg 400		
Ala	Gly	Ala	Cys	Va1 405	Val	Thr	Val	Lys	Leu 410								
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											atc Ile						40

											tac Tyr	96
											gac Asp	144
											aac Asn	192
											ctc Leu	240
											atc Ile 95	288
 			_		_	 					ccc Pro	336
 		_									gtg Val	384
											ctc Leu	432
	Lys	-	Thr	Ile	Gln	 Val	Leu	Arg	Ala	Gly	tcc Ser	480
											tac Tyr 17.5	528
											ctg Leu	576

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										atc Ile			624
	-	-	_				-		 -	ctg Leu 220	-	 	672
	-			_		-				atg Met			720
										ctc Leu			768
										gca Ala			816
										cag Gln			864
					_			-		cct Pro 300			912
			-	-						aag Lys			960
				-	Phe			_	Leu	cag Gln			1008
			_	_				-		ctc Leu			1056
_		_		_		_				act Thr			1104

													gcg Ala			1152
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			-	_		_	-	_			_		cgg Arg 415			1248
							_						atc Ile			1296
_		_				_		_	-	-			cag Gln	-		1344
													ttc Phe			1392
			_	_	-	-	-		_	_	_		ctg Leu			1440
				-	-		-	-					aac Asn 495			1488
					-								tgt Cys	-	:	1536
					-		-	-	-			-	acc Thr	-	:	1584
-	_	_			_		_		_	_		_	ctg Leu	-		1632

cag cag ttc tga 1644 Gln Gln Phe * 545

14

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			260					265					270		
Leu	Leu	Val 275	Asp	Val	Phe	Asp	Gly 280	Pro	Ala	Ala	Gln	Pro 285	Ser	Leu	Gly
Pro	Thr 290	Pro	Glu	Glu	Ala	Phe 295	Leu	Ser	Pro	Gly	Pro 300	Glu	Asp	Ile	Gly
Pro 305	Pro	Ile	Pro	Glu	Ala 310	Asp	Glu	Leu	Leu	Asn 315	Lys	Phe	Val	Cys	Lys 320
Asn	Asn	Gly	Val	Leu 325	Phe	Glu	Asn	Gln	Leu 330	Leu	Gln	Ile	Gly	Val 335	Lys
Ser	Glu	Phe	Arg 340	Gln	Asn	Leu	Gly	Arg 345		Tyr	Leu	Phe	Tyr 350	Gly	Asn
Lys	Thr	Ser 355	Val	Gln	Phe	Gln	Asn 360	Phe	Ser	Pro	Thr	Val 365	Val	His	Pro
Gly	Asp 370	Leu	Gln	Thr	Gln	Leu 375	Ala	Val	Gln	Thr	Lys 380	Arg	Val	Ala	Ala
G1n 385	Val	Asp	Gly	Gly	Ala 390	Gln	Val	G1n	Gln	Va1 395	Leu	Asn	Пе	Glu	Cys 400
Leu	Arg	Asp	Phe	Leu 405	Thr	Pro	Pro	Leu	Leu 410	Ser	Val	Arg	Phe	Arg 415	Tyr
Gly	Gly	Ala	Pro 420	Gln	Ala	Leu	Thr	Leu 425	Lys	Leu	Pro	Val	Thr 430	Ile	Asn
Lys	Phe	Phe 435	Gln	Pro	Thr	Glu	Met 440	Ala	Ala	Gln	Asp	Phe 445	Phe	Gln	Arg
Trp	Lys 450	Gln	Leu	Ser	Leu	Pro 455	Gln	Gln	Glu	Ala	G1n 460	Lys	Ile	Phe	Lys
Ala 465	Asn	His	Pro	Met	Asp 470	Ala	Glu	Val	Thr	Lys 475	Ala	Lys	Leu	Leu	Gly 480
Phe	Gly	Ser	Ala	Leu 485	Leu	Asp	Asn	Val	Asp 490	Pro	Asn	Pro	Glu	Asn 495	Phe
			500					505					510	Cys	
Leu	Arg	Leu 515	Glu	Pro	Asn	Ala	G1n 520	Ala	G1n	Met	Tyr	Arg 525	Leu	Thr	Leu
Arg	Thr 530	Ser	Lys	Glu	Pro	Val 535	Ser	Arg	His	Leu	Cys 540	Glu	Leu	Leu	Ala
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17

							aca Thr 175		528
							cct Pro		576
							act Thr		624
							gaa Glu		672
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<211> 236

<212> PRT

<213> Homo sapiens

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	130					135					140					
Ser 145	Ile	Met	Ile	Gly	Val 150	Lys	Pro	Cys	Ile	Asp 155	Lys	Ser	Val	Met	Glu 160	
Ser	Ser	Asp	Arg	Cys 165	Ala	Leu	Ser	Ser	Pro 170	Ser	Leu	Ala	Phe	Thr 175	Pro	
Pro	Ile	Lys	Thr 180	Leu	Gly	Thr	Pro	Thr 185	Gln	Pro	Gly	Ser	Thr 190	Pro	Arg	
Ile	Ser	Thr 195	Met	Arg	Pro	Leu	Ala 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	He	Ser	Asp 215	Arg	G1n	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	
Leu 225	Val	Ser	Lys	Ala	Met 230	Glu	Tyr	Met	Phe	Gly 235	Trp				•	
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											aag Lys					40
											act Thr					96
											ctg Leu					144
											aaa Lys 60					192
											aga Arg					240

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19

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						act Thr							2	88
-			_	-	_	aat Asn	-						3	36
						cat His							3	84
-	-					tat Tyr 135							4	32
				-		att Ile	_						4	80
						aaa Lys							5	28
			-		-	aaa Lys			_	-	-		5	76
-	-		_	-		ctc Leu	-	-					6	24
	aag Lys 210		taa *										6	36
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 $<\!\!400\!\!>10$ Met Gln Leu Ser Leu Thr Gln Ala Arg Thr Trp Lys Gly Leu Leu Leu

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Asp	Gln	Met 35	Ser	Asn	Glu	Glu	Leu 40	Tyr	Asp	Asn	Ļeu	Leu 45	Ser	Cys	Ser		
His	Arg 50	Thr	His	۷a٦	Val	Ala 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	Asp	Leu		
Asn 65	Val	Ala	Glu	Arg	Arg 70	Cys	Phe	Lys	Asn	Lys 75	Arg	Asn	Asn	Thr	Cys 80		
His	Thr	Thr	Ser	Thr 85	His	Thr	Ala	Lys	Thr 90	Asn	Glu	Asp	Leu	Leu 95	Lys		
Val	Ile	Ile	Ser 100	Val	Ser	Asn	Ala	Trp 105	Ile	Tyr	Pro	Leu	Lys 110	Met	Leu		
Ile	Pro	Ala 115	Val	Leu	Thr	His	Leu 120	61y	Ser	Tyr	Asp	Gly 125	Met	Met	Ala		
Arg	Ala 130	Ile	Glu	Leu	Asn	Tyr 135	Gly	Asn	Gln	Lys	Ile 140	Leu	Glu	Gly	Ala		
Lys 145	Phe	Leu	Leu	Ser	Arg 150	He	Gln	Pro	Gly	Ile 155	Glu	Glu	Asn	Asp	Tyr 160		
Pro	۷al	Trp	Ser	Ser 165	Leu	Lys	Glu	Leu	Arg 170	Ser	Ser	Asn	Lys	Ser 175	Ile		
His	Leu	Phe	Ala 180	Phe	Cys	Lys	Phe	Phe 185	Tyr	Cys	Leu	Arg	Lys 190	Asp	Thr		
Lys	Lys	Ile 195	Lys	Asp	Tyr	Leu	G1n 200	Пe	Leu	Arg	Pro	Asn 205	Ile	Ile	Lys		
Asn	Lys 210	Trp															
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		212> 213>		o sap	oiens	5											
		220> 221>	CDS														
				(6	551)												
		1 00>															
											gcg Ala					2	18
cct Pro	_	-				_					aac Asn					Ğ	96

22

651

195 200 205

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<211> 216

<212> PRT

<213> Homo sapiens

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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro 65 70 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro
100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val

Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro
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Lys Val Lys Lys Glu Arg Asp Pro 210 215

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24

468

48

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Pro Cys Thr Ser Val Gly Leu Phe Asn Phe Leu Cys Ser Arg Phe Tyr
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Leu Thr Lys Phe Asn Lys Glu Asn Asn Cys Val Leu Pro His Ser Lys
Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
                        55
Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro
                                        75
                    70
Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr
                                105
                                                     110
Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
                            120
                                                 125
Val Phe Leu Glu Leu Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu
                        135
Ser Gly Glu Asn Gly Asp Glu Val Lys Lys Glu
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			gag Glu													192
			ctg Leu													240
			tcc Ser													288
			gag Glu 100													336
			gag Glu													384
			gct Ala													432
			ctc Leu													480
			gca Ala													528
agc Ser	cct Pro	ggc Gly	agc Ser	ctc Leu	ctg Leu	gac Asp	acc Thr	atc Ile	gag Glu	gac Asp	tta Leu	gga Gly	gat Asp	gac Asp	cct Pro	576

26

.

180 185 190 624 gcc ctg agt cta agg tcc agc aca aac ccg gca gat tcc cgg aca gag Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 195 200 205 gct tct gag gat gac atg gga gac aaa gct ccc aag agg gcc aaa ccc 672 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 210 215 220 atc aaa aaa gcg ccc aaa gct gag cca ctg gct tcc aag aca ctg aag 720 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 225 230 235 240 765 acc cgg ccc aag aag acc tct ggc ggg ggc gac tca gct tga Thr Arg Pro Lys Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala * 245 250 <210> 16 <211> 254 <212> PRT <213> Homo sapiens <400> 16 Met Val Ser Trp Ile Ile Ser Arg Leu Val Val Leu Ile Phe Gly Thr 15 Leu Tyr Pro Ala Tyr Ser Ser Tyr Lys Ala Val Lys Thr Lys Asn Val 25 Lys Glu Tyr Val Lys Trp Met Met Tyr Trp Ile Val Phe Ala Phe Phe 40 Thr Thr Ala Glu Thr Leu Thr Asp Ile Val Leu Ser Trp Phe Pro Phe Tyr Phe Glu Leu Lys Ile Ala Phe Val Ile Trp Leu Leu Ser Pro Tyr 70 75 Thr Lys Gly Ser Ser Val Leu Tyr Arg Lys Phe Val His Pro Thr Leu 90 Ser Asn Lys Glu Lys Glu Ile Asp Glu Tyr Ile Thr Gln Ala Arg Asp 110 105 Lys Ser Tyr Glu Thr Met Met Arg Val Gly Lys Arg Gly Leu Asn Leu 125 120 Ala Ala Asn Ala Ala Val Thr Ala Ala Ala Lys Gly Gln Gly Val Leu 135 Ser Glu Lys Leu Arg Ser Phe Ser Met Gln Asp Leu Thr Leu Ile Arg

145	03	۸	۸٦؞	Laur	150	Lau	C1 5	^ ~ ~	Dwo	155 Asp	Clv	Ana	1 ou	۸na	160	
•				165	Pro				170					175		
Ser	Pro	Gly	Ser 180	Leu	Leu	Asp	Thr	Ile 185	Glu	Asp	Leu	Gly	Asp 190	Asp	Pro	
Ala	Leu	Ser 195		Arg	Ser	Ser	Thr 200		Pro	Ala	Asp	Ser 205	Arg	Thr	Glu	
Ala	Ser 210		Asp	Asp	Met	Gly 215		Lys	Ala	Pro	Lys 220		Ala	Lys	Pro	
I1e 225		Lys	Ala	Pro	Lys 230	Ala	Glu	Pro	Leu	Ala 235	Ser	Lys	Thr	Leu	Lys 240	
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					aca Thr											96
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					cgt Arg		Glu									192

gag Glu 65	cga Arg	ccg Pro	ggc Gly	cag Gln	gag Glu 70	ctg Leu	acc Thr	gat Asp	gtt Val	aat Asn 75	999 Gly	gtc Val	cgg Arg	att Ile	gca Ala 80	240
											gat Asp					288
gac Asp	ctc Leu	atc Ile	act Thr 100	ggt Gly	ggc Gly	atc Ile	atc Ile	aca Thr 105	gaa Glu	ctg Leu	999 Gly	gtc Val	ttt Phe 110	gcc Ala	cct Pro	336
gag Glu	gag Glu	ctc Leu 115	cgg Arg	aca Thr	gcc Ala	cta Leu	acc Thr 120	acc Thr	acc Thr	atc Ile	tct Ser	tcc Ser 125	agg Arg	gat Asp	gga Gly	384
	cta Leu 130						taa *									408
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	Ala	Asn	Xaa 20		Thr	Ala	Asn	Lys 25		Gly	Thr	Tyr	Gln 30		Ala	
Пе	Val	Ala 35		His	His	Gly	Ile 40		Phe	Tyr	Val	Ala 45		Pro	Ser	
Ser	Ser 50		Asp	Leu	Arg	Leu 55		Thr	Gly	Lys	Glu 60		Ile	Ile	Glu	
65	Aṛg				70	Leu				75	Gly				80	
Ala	Pro	Gly	Ile	G7y 85	Val	Trp	Asn	Pro	A7a 90	Phe	Asp	Val	Thr	Pro 95	His	

Asp	Leu	Пе	Thr 100	Gly	Gly	Пе	Пе	Thr 105	Glu	Leu	Gly	Val	Phe 110	Ala	Pro	
Glu	Glu	Leu 115	Arg	Thr	Ala	Leu	Thr 120		Thr	Ile	Ser	Ser 125		Asp	Gly	
Thr	Leu 130	Asp	Gly	Pro	Gln	Met 135			,				•		•	
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Met 1	Gly	Asn	Phe	Arg 5	Gly	His	Ala	Leu	Pro 10	Gly	Thr	Phe	Phe	Phe 15	Ile	
			tgg Trp 20													96
			cga Arg													144
			ttg Leu													192
atg Met 65	gct Ala	999 Gly	gag Glu	cag Gln	ttt Phe 70	att Ile	cct Pro	gga Gly	ggg Gly	ccc Pro 75	cat His	ctg Leu	atg Met	tta Leu	tat Tyr 80	240
			caa Gln													288
			ttc Phe 100													336

ttc Phe	acc Thr	atc Ile 115	agt Ser	tca Ser	ctt Leu	cct Pro	gtg Val 120	tcc Ser	tta Leu	acc Thr	aag Lys	tta Leu 125	atg Met	ttg Leu	tca Ser	384
											aac Asn 140					432
											ctg Leu					480
											ctt Leu					528
											ctg Leu					576
											ccc Pro					624
											ttt Phe 220					672
											gtt Val					.720
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-	gaa Glu	_	tga *													828

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						gag Glu										240
						gag Glu										288
						aga Arg										336
gag	ttt	gaa	tcc	cag	agc	cct	agg	tat	gaa	ccc	caa	agc	cct	ggc	tat	384

Glu	Phe	Glu 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	G1u	Pro	Gln	Ser 125	Pro	Gly	Tyr	
_			_	ccc Pro			_									432
				tat Tyr												480
	-			gct Ala 165		-										528
	_			gan Xaa	-	_	_									·576
				tcc Ser												624
_				999 Gly					-							672
		-		ttt Phe		-										720
_		_		cca Pro 245							-				-	768
				aac Asn												816
				atc Ile												864
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc	912

Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Aìa	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu	
								ggc Gly								960
								agc Ser								1008
								tac Tyr 345	-						_	1056
								ctg Leu								1104
					-	-		gag Glu	-		_	-		-	_	1152
								agg Arg								1200
					-		-	agc Ser			-		-	-		1248
				_	_		-	cgg Arg 425		_			-	-		1296
						Gly	_	agc Ser	_		_				-	1344
Arg								tac Tyr								1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	Gln	Arg	Ser	His	Thr 480	
	gag Glu					_								-	_	1488
	tcc Ser															1536
	aag Lys															1584
	cgc Arg 530											tga *				1623
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Ser	Glu	Asn 35		Glu	G1u	Glu	Ile 40		Gln	Gln	Glu	Gly 45		Gly	Asp	
Tyr	Glu 50		Glu	Glu	Пe	Pro 55		Gly	Leu	Glu	Pro 60		Ser	Pro	Gly	
Phe 65	G1u	Pro	Gln	Ser	Pro 70		Phe	Glu	Pro			Pro	Arg	Phe		
	Glu	Ser	Pro	-		Glu	Ser	Arg		75 Pro	Gly	Leu	Val		80 Pro	
Ser	Pro	Glu	Phe	85 Ala	Pro	Arg	Ser	Pro	90 Glu	Ser	Asp	Ser	G1n	95 Ser	Pro	

			100					105					110		
Glu	Phe	Glu 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	G1n	Ser 125	Pro	Gly	Tyr
Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
145			Arg	-	150					155					160
			Glu	165					170					175	
			Pro 180					185					190	_	
		195	Asp				200					205			•
	210		Ile			215					220				
225			Gln		230					235					240
			Gly	245		_			250				_	255	
•		_	Pro 260			•	-	265	•	-	-		270		J
		275	Leu				280					285			
	290		Glu		-	295			1		300			·	
305			Gln		310			-		315		_	-	_	320
			Lys	325					330					335	
			Ser 340			-		345	•				350	-	
		355	Asp				360					365			
	370		Pro			375					380				
Asn 385	Ser	Ser	Leu	Arg	Ser 390	His	Gln	Arg	Val	His 395	Thr	Gly	Gln	Arg	Pro 400
Phe	Ser	Cys	Gly	Ile 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
Пе	Pro	His	Ala 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	Gly 435	Lys	Arg	Phe	Gly	Gln 440	Ser	Ser	Va1	Leu	Ala 445	Ile	His	Ala
Ara	Thr	His	Leu	Pro	Glv	Ara	Thr	Tvr	Ser	Cvs	Pro	Asp	Cvs	Glv	Lvs

	450					455					460					
Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Ile	Gln	His 475	G1n	Arg	Ser	His	Thr 480	
Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg	
Ser	Ser	Thr	Leu 500	Leu	Gln	His	His	Arg 505	Val	His	Ser	Gly	Glu 510	Arg	Pro	
Tyr	Lys	Cys 515	Asp	Asp	Cys	Gly	Lys 520	Ala	Phe	Ser	G]n	Ser 525	Ser	Asp	Leu	
Пe	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg	Arg 540					
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						cag Gln										96
						atc Ile										144
						gcg Ala 55										192
						gag Glu	-	-			_	_	_	_		240
						cac His										288

85 90 95 aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cgc 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly * 130 135 140

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<211> 143

<212> PRT

<213> Homo sapiens

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 Ile Leu Ile Gln Thr Asn Gln Leu Thr 20
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 Leu His Tyr 30

 Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp 35
 40
 45

 Cys Thr Val Ser Thr Gly Ala Ala Ala Ala Met Met Ala Val Arg Val Leu 50
 55
 60

 Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu 65
 70
 75
 80

 Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 85
 90
 95

 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100
 105
 110

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Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly

135

140

<210> 25

130

<211> 912

<212> DNA

<213> Homo sapiens

PCT/US00/29052

WO 01/29221

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145				150					155				160	
		-				-	-		-		_	acg Thr 175	ttg Leu	528
-	-	_	 -						-	_		cca Pro	-	576
-			_			-						att Ile	_	624
												act Thr		672
	_				_			_	_		 	gag Glu	~	720
	_			-			-				_	tgt Cys 255	-	768
												gga Gly		816
												gag Glu		864
_	tgc Cys 290		_		-	-	_	-	_			ccc Pro	tga *	912

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<211> 303

<212> PRT

<213> Homo sapiens

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<211> 795

<212> DNA

<213> Homo sapiens

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					gag Glu											144
				_	ttg Leu			-	_			_		-		192
					atc Ile 70											240
					gaa Glu	-		_			_					288
_	-				gag Glu	-		-		-	-				~	336
					cgc Arg	-	_	_		-	_	-		_		384
_					gaa G1u	_	-	-		_				_		432

	130					135					140						
						_		-			ttt Phe		-				480
	_		-					-		-	agt Ser	_	-	-	_		528
				~ ~							aaa Lys						576
			-		_					_	aaa Lys		-		_		624
-				-							tcc Ser 220						672
											ttg Leu					,	720
-			-		-		-	-	-	-	gaa Glu	-	-				768
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<213> Homo sapiens

<220>

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<211> 711

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

PCT/US00/29052

<222> (1)...(711)

WO 01/29221

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						ggg Gly										144
						gat Asp 55										192
						gag Glu										240
						ggt Gly										288
						ggt Gly										336
				_	-	att Ile										384
						gaa Glu 135										432
						gtc Val										480
cag	ctg	gct	gga	ctg	aca	ttg	ttg	aca	aac	atg	act	gtt	acc	aat	gac	528

Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp		
			_			-				gac Asp	-		_			57	'6
						_	_			gtt Val					_	62	24
	-						_		-	gga Gly			-	-		67	'2
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<211> 236

<212> PRT

<213> Homo sapiens

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										•						
Ser 145	G1n	Val	Cys	Glu	Asp 150	Val	Phe	Ser	Gly	Pro 155	Leu	Asn	Ser	Ala	Val 160	
Gln	Leu	Ala	G1y	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175		
His	GIn		Met 180	Leu	His	Ser	Tyr	Ile 185	Thr	Asp	Leu	Phe	Gln 190	Val	Leu	
		195		_			200					205		Leu		
	210					215				·	220	Leu	Arg	Ala	Gln	
Va1 225	Asp	Ser	Ser	Phe	Leu 230	Ser	Leu	Met	Thr	Ala 235	Thr					
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														atg Met		192
														atg Met		240
cag	gag	tgg	ctg	gcg	gct	gtg	ggc	gat	gac	tat	gct	gct	gtg	gtc	tgg	288

Gln	Glu	Trp	Leu	A1 a 85		Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Va1	Val 95		
				Glu					Pro		gaa Glu			Pro		336
			Lys					Phe		-	gag Glu		-	-	-	384
											tat Tyr 140					432
											ctg Leu					480
											gac Asp					528
											ggc Gly					576
											cgc Arg					624
cgt Arg	gtc Val 210	ccc Pro	atg Met	gtc Val	cac His	tcc Ser 215	acc Thr	ttc Phe	ctt Leu	gca Ala	tcc Ser 220	ctg Leu	cgg Arg	gct Ala	gaa Glu	672
											ccc Pro					720
								Ala			tgc Cys					768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	сас	cgt	tat	ggg	tac	atg	aat	gtg	<u></u> 816

Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
	gtg Val				_	-	_	_	-	-		-				864
	ctg Leu 290						-						_	-		912
	cat His															960
	gtc Val															1008
	ctc Leu						-							-	-	1056
	gtg Val															1104
	gac Asp 370			_			-	-							-	1152
	aag Lys					-			-						_	1200
	gtg Val					-			-						-	1248
	cgc Arg															1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

Asn	Val	Glu	Ala	Glu	Lys	Leu	Ser	Trn	Asn	Leu	Πe	Tvr	Leu	G] v	Ara	
,	,	435	,,, 4	4,4	_,,,	200	440	,, ρ	7159	Lou	110	445	LCU	uij	7 ii g	
	Gln				gag Glu	Lys										1392
	450					455			•		460					
Leu					tac Tyr					Leu					Arg	1440
465					470					475					480	
					aag Lys											1488
				485					490					495		
			-		ttc Phe	-			_		_	-				1536
			500					505					510		*	
					cac His											1584
414	4 ,111	515	_,5	711 C	7115	1110	520	110		ЛЭР	LCG	525	/ t i G	THE	JCI	
					gct Ala											1632
ATU .	530	110	LCu	LCu	Aia	535	110	(11)	1113	131	540	uiy	yoh	Ala	ara	
					gag											1680
545	Leu	Set	Ash	1111.	G1u 550	HIL	ser.	Sei.	Pro	555	ASP	ASP	ASP	261.	560	
					agc											1728
arg	Leu	116	ser	565	Ser	ыу	5er	uin	Lys 570	ınr	Leu	Arg	5er	Pro 575	Ala	
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Trp	Ihr	*														

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<211> 578

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<213> Homo sapiens

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Gly	Pro	Trp	Leu 20	Glu	Ala	Ala	Gly	Val 25	Ala ·	Glu	Ser	Pro	Leu 30	Pro	Ala
Val	۷al	Leu 35	Ala	Ile	Leu	Ala	Arg 40	Asn	Ala	Glu	His	Ser 45	Leu	Pro	His
Tyr	Leu 50	Gly	Ala	Leu	Glu	Arg 55	Leu	Asp	Tyr	Pro	Arg 60	Ala	Arg	Met	Ala
Leu 65	Trp	Cys	Ala	Thr	Asp 70	His	Asn	Val	Asp	Asn 75	Thr	Thr	Glu	Met	Leu 80
Gln	Glu	Trp	Leu	Ala 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Val 95	Trp
Arg	Pro	Glu	Gly 100	Glu	Pro	Arg	Phe	Tyr 105	Pro	Asp	Glu	Glu	Gly 110	Pro	Lys
His	Trp	Thr 115	Lys	Glu	Arg	His	Gln 120	Phe	Leu	Met	Glu	Leu 125	Lys	G1n	Glu
	130					135	·				140			Phe	
145					150					155				Leu	160
_				165					170					Thr 175	_
			180					185					190	Arg	
		195	_				200		_		_	205	-	Cys	
	210					215					220			Ala	
225		•			230					235				Thr	240
			•	245					250					A1a 255	
			260					265					270	Asn	
		275					280					285		Phe	
His	Leu 290	He	Leu	Glu	Ala	Leu 295	Val	Asp	Gly	Pro	Arg 300	Met	Gln	Ala	Ser
305				_	310		Ť	-		315				Phe	320
Glu	Val	Phe	Val	11e 325	Ser	Leu	Ala	Arg	Arg 330	Pro	Asp	Arg	Arg	G1u 335	Arg

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Met Leu Ala Ser Leu Trp Glu Met Glu Ile Ser Gly Arg Val Val Asp
                                345
Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
        355
                            360
Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
                                            380
                        375
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
                    390
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
               405
                                   410
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
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Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
                            440
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
                                            460
                       455
Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
                                        475
                   470
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
                                    490
               485
Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
                                505
Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
                            520
Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
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                        535
Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Asp Ser Gly
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Trp Thr
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<212> DNA

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<220>

<221> CDS

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WO 01/29221

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	gca Ala	_	_					-							-	96
_	gga Gly				_											144
	ctt Leu 50							_	_	_	-		•	_	_	192
	gga Gly															240
	agt Ser	-		_			-		_						_	288
	ctg Leu				-	-	-									336
	cct Pro															384
	tac Tyr 130		_			-					_		_	-		432
	gct Ala															480
	ttc Phe															528
atg	tat	gtg	ctt	gga	atg	gca	gaa	gaa	ttt	aaa	ggt	gaa	att	gca	gtc	576

WO 01/29221

Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	Glu 185	Phe	Lys	Gly	Glu	Ile 190	Ala	Val	
							gcc Ala 200						-		-	624
_						-	agc Ser	_	_	-			-			672
							ttc Phe									720
		-		-	_		atc Ile			-	-			-		768
	_	_		-			cca Pro				-			-		816
		-	-			-	gca Ala 280	-	-							864
	-	_		_			gaa Glu			_						912
							gaa Glu									960
							gcc Ala									1008
			-	-			acg Thr								-	1056
ggt	9 99	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 365

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<211> 383

<212> PRT

<213> Homo sapiens

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Asn	Phe	Val	Ile	Asp 245	Glu	Asn	Пe	Leu	Lys 250	Glu	Glu	Gly	Пе	G1u 255	Asn	
Phe	Asp	Val	Tyr 260		Пе	Lys	Pro	Gly 265	His	Pro	Leu	Gln	Pro 270		Phe	
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	Ala 280	Val	Ser	Lys	Lys	Val 285	Glu	Ser	Thr	
Gly	Ala 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys	Leu	G1n 300	Leu	Gln	Pro	Lys	
305		Ser	-		310					315				•	320	
		Asp		325					330					335		
		Gly	340	•	-			345					350			
-		Asn 355		-	-		360					365			Va]	
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn		
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		ggc Gly														96
	<i>-, -</i>	٠, ٦	20			-, -	1,0	25	5,5	J	- J -	-50	30			
		tcc Ser 35														144

				att Ile 55							-			192
				gtg Val									i	240
-	-	-		gac Asp	_							-	;	288
				gcc Ala	-								(336
_	-		 	agc Ser	_	-		-			_		(384
_				ttt Phe 135	-		-		_	 			4	432
				cct Pro									4	480
				tcc Ser									, (528
-		-		cac His				-				-	į	576
				cgt Arg									6	524
				ctg Leu 215									6	672

						agc Ser									720
-						tgt Cys	-	-	-				_	_	768
	_	-		-	-	cag Gln						_	_	_	816
_						atg Met		-			-			_	864
		Glu	_		_	aac Asn 295						-			912
						ccc Pro								-	960
						ctc Leu									1008
						gac Asp									1056
						atg Met									1104
						ggc Gly 375									1152
						ttc Phe						_	-		1200

			atg Met	_												124	8
			atc Ile 420											_	-	129	6
-			999 G1 <i>y</i>													134	4
	-	_	aac Asn	-	-		_	_								137	1
	<; <;	210> 211> 212> 213>	456	o sap	oiens	6											
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Met 1	<'a	221> 222> 223> 400>	(1). Xaa	(2 = Ar	ny Ar				Leu 10	Leu	Ser.	Cys	Ala	Ser 15	Cys		
1	<; <; <; Gly	221> 222> 223> 400> Ala	(1). Xaa 36 Cys	(4 = Ar Leu 5	ny Ar Gly	Ala	Cys	Ser Leu	10				Pro	15			
1 Leu	<td>221> 222> 223> 400> Ala Gly Ser</td> <td>(1). Xaa 36 Cys</td> <td>= Ar Leu 5 Ala</td> <td>Gly Pro</td> <td>Ala Cys</td> <td>Cys Ile Leu</td> <td>Ser Leu 25</td> <td>10 Cys</td> <td>Ser</td> <td>Cys</td> <td>Cys Phe</td> <td>Pro 30</td> <td>15 Ala</td> <td>Ser</td> <td></td> <td></td>	221> 222> 223> 400> Ala Gly Ser	(1). Xaa 36 Cys	= Ar Leu 5 Ala	Gly Pro	Ala Cys	Cys Ile Leu	Ser Leu 25	10 Cys	Ser	Cys	Cys Phe	Pro 30	15 Ala	Ser		
1 Leu Arg	<pre><? <pre><? <pre></pre> <pre></pre> <pre>Gly Cys Asn Val </pre>	221> 222> 223> 400> Ala Gly Ser 35	(1). Xaa 36 Cys Ser 20	= Ar Leu 5 Ala	Gly Pro Ser	Ala Cys Arg Ile	Cys Ile Leu 40	Ser Leu 25 Ile	10 Cys Phe	Ser Thr	Cys Phe Gly	Cys Phe 45	Pro 30 Leu	15 Ala Phe	Ser Leu		
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1 Leu Arg Gly Leu 65 Val	Gly Cys Asn Val 50 Tyr Leu	221> 222> 223> 400> Ala Gly Ser 35 Leu Lys	(1). Xaa 36 Cys Ser 20 Thr Val Leu	Leu 5 Ala Val Ser Pro His 85	Gly Pro Ser Ile Trp 70 Ile	Ala Cys Arg Ile 55 Val	Cys Ile Leu 40 Met Cys Cys	Ser Leu 25 Ile Leu Glu Gly	10 Cys Phe Ser Glu Ser 90	Ser Thr Pro Gly 75 Leu	Cys Phe Gly 60 Ala Leu	Cys Phe 45 Val Gly	Pro 30 Leu Glu Ile Tyr	15 Ala Phe Ser Pro Arg 95	Ser Leu Gln Thr 80 Ala		

		115					120					125			
Gln	Asn 130	Gly	Phe	Trp	Phe	Phe 135		Phe	Leu	Ile	Leu 140	Val	G1y	Leu	Thr
Val 145		Ala	Phe	Tyr	Ile 150	Pro	Asp	Gly	Ser	Phe 155	Thr	Asn	Пe	Trp	Phe 160
Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	He	Leu	Пe	Gln	Leu 175	Val
Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185	Asn	Gln	Arg	Trp	Leu 190	Gly	Lys
Ala	Glu	Glu 195	Cys	Asp	Ser	Arg	A1a 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
Thr	Leu 210	Leu	Phe	Tyr	Leu	Leu 215	Ser	Ile	Ala	Ala	Va7 220	Ala	Leu	Met	Phe
Met 225		Tyr	Thr	Glu	Pro 230	Ser	Gly	Cys	His	G1u 235	Gly	Lys	Val	Phe	Ile 240
			Leu	245		_		_	250					255	
			G1n 260					265					270		
		275	Leu				280					285			
	290		Gln			295					300			-	
305			Val		310					315				·	320
			Ile	325					330					335	
			Arg 340			•		345					350		
		355	Cys				360	•				365			
	370		Ala			375					380				
385			Ser	•	390					395					400
			Met	405					410					415	
			11e 420					425					430		
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	130				135				140				
							cca Pro					-	480
							acc Thr						528
-				_	-	-	gaa Glu 185			_	-	•	576
						-	ata Ile					-	624
							cag Gln						672
	Asp						caa Gln						720
			-	-			tta Leu	-	-		-		768
	-						ggt Gly 265						816
							gtt Val						864
							gag Glu						912
					-	-	aca Thr						960

305					310				315				320	
	-	-	•	_	-	aaa Lys	_					-	-	1008
						ggc Gly								1056
			-			gga Gly	-		-	_	-	-	 	1104
_	-	_			-	gac Asp 375		-	_					1152
			-	-		atg Met			-	-				1200
-	_		-			ttg Leu		_	-		_	_	_	1248
aga Arg	ctg Leu	tga *												1257

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<212> PRT

<213> Homo sapiens

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	50	*				55					60				
Gly 65	Gly	Lys	Ala	Leu	Pro 70	Cys	Пe	Val	Asp	Va1 75	Arg	Asp	Glu	Gln	G1r 80
Ile	Ser	Ala	Ala	Va1 85	Glu	Lys	Ala	Пe	Lys 90	Lys	Phe	Gly	Gly	Ile 95	Asp
Ile	Leu	Val	Asn 100		Ala	Ser	Ala	Ile 105		Leu	Thr	Asn	Thr 110	Leu	Asp
	•	115					120				Val	125			Ţ
	130					135					Leu 140				-
145					150					155	Asn				160
				165					170		Lys			175	
			180					185			Gly		190		
		195					200				Ala	205			
	210					215					Lys 220				
225					230					235	Lys				240
				245					250		Glu			255	
			260					265			Leu		270	·	
		275					280				Lys	285			
	290					295					G1n 300				-
305					310					315	Ile		-	•	320
				325					330		Ile			335	
Leu	Seŗ	Gly	G1u 340	Asp	Gly	Gly	Thr	Trp 345	Phe	Leu	Asp	Leu	Lys 350	Ser	Lys
Gly	Gly	Asn 355	Val	Gly	Tyr	Gly	G1u 360	Pro	Ser	Asp	Gln	Ala 365	Asp	Val	Val
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	G1y	Lys	Leu
Lys 385	Pro	Thr	Met	Ala	Phe 390	Met	Ser	Gly	Lys	Leu 395	Lys	Ile	Lys	Gly	Asn 400
Met	Δla	Leu	Δla	ΠA	Lvc	الم ا	Glu	Lvc	1 011	Mot	Δcn	Gln	Mat	Acn	۸la

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		115			120			125			
							gag Glu				432
							gag Glu 155				480
							aaa Lys				528
							tca Ser				576
							gat Asp				624
taa *	÷										627

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 Met
 Val
 Phe
 Tyr
 Phe
 Thr
 Ser
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 Asn
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 Ala
 Tyr
 Thr

 I le
 Tyr
 Met
 Gly
 Lys
 Asp
 Lys
 Tyr
 Glu
 Asn
 Glu
 Asp
 Leu
 Ile
 Lys
 His
 Val
 Asp
 Lys
 Leu
 His
 Val
 Asp
 Lys
 Leu
 His
 Lys
 Gly
 Glu
 Asn
 Ile
 Pro
 Asn
 Asn
 Ile
 Ile
 Pro
 Asn
 Ile
 Asn
 Ile
 Ile

				85					90					95		
Asn	Leu	Lys	Lys 100	Thr	Ala	Asp	Met	Asp 105		Gly	Gln	Ile	Gly 110	Phe	His	
Arg	Gln	Lys 115		Val	Lys	Ile	Val 120		Val	Glu	Lys	Lys 125		Asn	Glu	
Ile	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	Val	Glu	Arg 140	Phe	Pro	Asp	Leu	
145					150					155				-	Lys 160	
				165					170		Glu			175		
			180	•				185			Ser		190			
Glu	Asn	Met 195	Ser	Ser	Asn	Gln	Asp 200	Gly	Asn	Asp	Ser	Asp 205	Glu	Phe	Met	
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											gtc Val					. 96
											nag Xaa					144
											999 Glу					192

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Pro 65	Gln	Cys	Gly	Phe	Ser 70		Ala	Val	Val	G1n 75		Leu	Arg	Ļeu	His 80	
Gly	Val	Arg	Asp	Tyr 85		Ala	Tyr	Asn	Va1 90	Leu	Asp	Asp	Pro	GՂu 95		
Arg	Gln	Gly	Ile 100		Asp	Tyr	Ser	Asn 105	Trp	Pro	Thr	Ile	Pro 110		Val	
Tyr	Leu	Asn 115		Glu	Phe	Va1	Gly 120	Gly	Cys	Asp	Ile	Leu 125	Leu	Gln	Met	
His	Gln 130	Asn	Gly	Asp	Leu	Val 135	Glu	Glu	Leu	Lys	Lys 140		Gly	Ile	His	
Ser 145		Leu	Leu	Asp	G1u 150	_	Lys	Asp	G1n	Asp 155		Lys				·
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								Trp								40
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								cgc Arg								144
								cag Gln								192
cct Pro 65	cag Gln	acg Thr	gga Gly	ggt Gly	acc Thr 70	tgg Trp	gag Glu	tca Ser	cag Gln	tgg Trp 75	tcc Ser	aag Lys	acc Thr	tcg Ser	cag G1n 80	240

				ggt Gly								gaa Glu	288
				tac Tyr						-		_	336
				att Ile		_			-	_			384
				cgt Arg 135									432
				aac Asn									480
			Ser	gtg Val									528
				tgt Cys									576
	-		-	gga Gly	-		-	_		_		_	624
		_		atg Met 215			-			-	•		672
		Thr		aat Asn									720
	Asn			gaa Glu		Pro							768

									tcc Ser							816
			Пe			_			acg Thr						_	864
									gct Ala							912
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Gly	Ala	Gly	Ala 20	Cys	Tyr	Cys	Ile	Tyr 25	Arg	Leu	Thr	Arg	Gly 30	Arg	Arg	
Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40		Ser	Ser	Lys	Ser 45		Gly	Ala	
Leu	G1u 50		Gly	Thr	Ser	G1u 55		Gln	Leu	Cys	Gly 60	-	Ser	Ala	Arg	
Pro 65		Thr	Gly	Gly	Thr 70		Glu	Ser	Gln	Trp 75		Lys	Thr	Ser	G1n 80	
	G1u	Asp		Thr 85	-	Gly	Ser	Tyr	Asp 90		Val	Leu	Asn	A1 a 95		

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Gln Leu Gln Lys Leu Leu Tyr Leu Leu Glu Ser Thr Glu Asp Pro Val
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Ile Ile Glu Arg Ala Leu Ile Thr Leu Gly Asn Asn Ala Ala Phe Ser
                            120
Val Asn Gln Ala Ile Ile Arg Glu Leu Gly Gly Ile Pro Ile Val Ala
                        135
                                            140
Asn Lys Ile Asn His Ser Asn Gln Ser Ile Lys Glu Lys Ala Leu Asn
                    150
Ala Leu Asn Asn Leu Ser Val Asn Val Glu Asn Gln Ile Lys Ile Lys
                                    170
Ile Tyr Ile Ser Gln Val Cys Glu Asp Val Phe Ser Gly Pro Leu Asn
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                                185
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Ser Ala Val Gln Leu Ala Gly Leu Thr Leu Leu Thr Asn Met Thr Val
                            200
                                                 205
Thr Asn Asp His Gln His Met Leu His Ser Tyr Ile Thr Asp Leu Phe
                        215
                                            220
Gln Val Leu Leu Thr Gly Asn Gly Asn Thr Lys Val Gln Val Leu Lys
                    230
                                        235
Leu Leu Leu Asn Leu Ser Glu Asn Pro Ala Met Thr Glu Gly Leu Leu
                245
                                    250
Arg Ala Gin Val Asp Ser Ser Phe Leu Ser Leu Tyr Asp Ser His Val
            260
                                265
                                                     270
Ala Lys Glu Ile Leu Leu Arg Val Leu Thr Leu Phe Gln Asn Ile Lys
                            280
Asn Cys Leu Lys Ile Glu Gly His Leu Ala Val Gln Pro Thr Phe Thr
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                                            300
Glu Gly Ser Leu Phe Phe Leu Leu His Gly Glu Glu Cys Ala Gln Lys
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Ile Arg Ala Leu Val Asp His His Asp Ala Glu Val Lys Glu Lys Val
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Val Thr Ile Ile Pro Lys Ile
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		tta Leu						-				_		-		192
		gac Asp										-			_	240
		tcc Ser							-		-	_			-	288
		aag Lys														336
		atc Ile 115														384
		atc Ile														432
		gga Gly														480
gaa	tat	aag	ccc	ctt	tcg	ggc	att	cgg	tac	atg	tgg	tcg	tac	cat	tta	528

Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu	
						agt Ser									_	576
						gnt Xaa										624
						atc Ile 215										672
						gtg Val										720
						gtc Val										768
						agg Arg										816
						tac Tyr						-		_		864
						999 Gly 295										912
				Leu		aag Lys			Ser							960
			Asp			att Ile		Leu								1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	Ala 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe	
									gta Val							1104
									gaa Glu							1152
				Ala					aca Thr							1200
									ctg Leu 410							1248
									cag Gln							1296
								-	att Ile	-	-	tag *				1335
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Leu	ser	Leu	Ala 20	Met	Met	Phe	Thr	Phe 25	Arg	Phe	He	Ihr	Thr 30	Leu	Leu	
Val	His	Пе		Пe	Ser	Leu	Val		Leu	Gly	Leu	Leu		Val	Cys	

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Ile
Glu 65	Leu	Asp	Thr	Glu	Arg 70	Glu	Asn	Met	Lys	Cys 75	Val	Leu	Gly	Phe	Ala 80
Пe	Val	Ser	Thr	G]y 85	Пe	Thr	Ala	Val	Leu 90	Leu	Val	Leu	He	Phe 95	Val
Leu	Arg	Lys	Arg 100	Ile	Lys	Leu	Thr	Val 105	Glu	Leu	Phe	Gln	Ile 110	Thr	Asn
Lys	Ala	Ile 115	Ser	Ser	Ala	Pro	Phe 120	Leu	Leu	Phe	Gln	Pro 125	Leu	Trp	Thr
Phe	Ala 130	Ile	Leu	Пe	Phe	Phe 135	Trp	Val	Leu	Trp	Val 140	Ala	Val	Leu	Leu
Ser 145	Leu	Gly	Thr	Ala	Gly 150	Ala	Ala	Gln	Val	Met 155	Glu	Gly	Gly	Gln	Val 160
Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Пe	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu
Пe	Gly	Leu	Ile 180	Trp	Thr	Ser	Glu	Phe 185	Ile	Leu	Ala	Cys	Gln 190	Gln	Met
Thr	Ile	Ala 195	Gly	Ala	Val	Xaa	Thr 200	Cys	Tyr	Phe	Asn	Arg 205	Ser	Lys	Asn
Asp	Pro 210	Pro	Asp	His	Pro	Ile 215	Leu	Ser	Ser	Leu	Ser 220	Ile	Leu	Phe	Phe
Tyr 225	His	Gln	Gly	Thr	Ile 230	Val	Lys	Gly	Ser	Phe 235	Leu	Ile	Ser	Val	Va1 240
Arg	Ile	Pro	Arg	Ile 245	Ile	Val	Met	Tyr	Met 250	Gln	Asn	Ala	Leu	Lys 255	Glu
Gln	His	Gly	Ala 260	Leu	Ser	Arg	Tyr	Leu 265	Phe	Arg	Cys	Cys	Tyr 270	Cys	Cys
Phe	Trp	Cys 275	Leu	Asp	Lys	Ţyr	Leu 280	Leu	His	Leu	Asn	G1n 285	Asn	Ala	Tyr
Thr	Thr 290	Thr	Ala	Ile	Asn	Gly 295	Thr	Asp	Phe	Cys	Thr 300	Ser	Ala	Lys	Asp
305					310	•				His 315					320
Cys	Phe	Gly	Asp	Phe 325	Ile	He	Phe	Leu	G1y 330	Lys	Val	Leu	Val	Val 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Val	Ala	Phe	Phe 365	Ala	Tyr	Leu
Val	Ala 370	His	Ser	Phe	Leu	Ser 375	Val	Phe	G1u	Thr	Val 380	Leu	Asp	Ala	Leu
Phe	Leu	Cvs	Phe	Ala	Val	Asp	Leu	Glu	Thr	Asn	Asp	G] v	Ser	Ser	Glu

385					390					395					400	
Lys	Pro	Tyr	Phe	Met 405		Gln	Glu	Phe	Leu 410		Phe	Val	Lys	Arg 415	Ser	
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Asn	Glu	G1u 435		Thr	Glu	Leu	G1n 440		He	Val	Arg					
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				tcc Ser												96
				gaa Glu												144
				aaa Lys												192
atg Met 65	aag Lys	ttc Phe	att Ile	tgt Cys	aaa Lys 70	gat Asp	ttt Phe	tgg Trp	act Thr	acg Thr 75	gta Val	ttc Phe	aag Lys	aaa Lys	caa Gln 80	240
				agg Arg 85												288
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Met Lys Lys Cys Leu Leu Pro Val Leu Ile Thr Cys Met Gln Thr Ala

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				Arg					Met					Asn	tac Tyr	96
			Glu												gga Gly	144
aat Asn	gca Ala 50	Thr	gca Ala	tcc Ser	cag Gln	gaa Glu 55	ctt Leu	ggt Gly	tat Tyr	ggt Gly	tgt Cys 60	ctc Leu	aag Lys	ttc Phe	ggc Gly	192
						gtg Val										240
tta Leu	gat Asp	gga Gly	att Ile	gag Glu 85	tgt Cys	gcc Ala	agt Ser	cct Pro	agg Arg 90	acc Thr	ttt Phe	cta Leu	cga Arg	gaa Glu 95	aat Asn	288
						acc Thr										336
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						999 Gly 135										432
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<211> 171

<212> PRT

<213> Homo sapiens

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<220>

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<222> (1)...(870)

<400> 51

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			aag Lys					Phe		144
			gat Asp 55							192
			gaa Glu							240
			aca Thr			-	-		-	288
			cct Pro							336
			gtt Val							384
			ctg Leu 135			_		-	 _	432
			ctg Leu							480
			gag Glu							528
			gag Glu	Asn						576
			gac Asp							624

		tca Ser								-	_	tgt Cys	 672
		tac Tyr									_		720
		tac Tyr	-	_		_	-	-	_		~ ~		768
		tcc Ser										~	816
		cac His 275											864
ccg Pro	tga *												870

<210> 52

<211> 289

<212> PRT

<213> Homo sapiens

<400> 52

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 Leu
 Leu
 Leu
 Val
 His
 Gly
 Ser
 Pro
 Leu
 Val
 Phe
 Gly
 Gly
 Gly
 Jeu
 Val
 Phe
 Arg
 Leu
 Val
 His
 Gly
 Ser
 Pro
 Leu
 Val
 Phe
 Arg
 Arg
 Arg
 Arg
 Leu
 Val
 Phe
 Tyr
 Cys
 His
 Phe
 Pro
 Arg
 Arg</th

100 105 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro 120 Lys Gly Lys Lys Phe Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys 135 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly Arg 150 155 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly 165 170 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys 185 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg 200 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys 215 220 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu 230 235 Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro 245 250 Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp 265 Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His 275 280 Pro

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								agt Ser			288
								ttc Phe			336
								gcc Ala 125			384
								aac Asn			432
								cgc Arg			480
								gaa Glu			528
								gag Glu			576

cac His	att Ile	Cag Gln 195	Arg	ctc Leu	cag Gln	gct Ala	gag G1u 200	Glu	cag G1n	cag Gln	aaa Lys	gcc Ala 205	Pro	999 Gly	gag Glu	624
		Asp			gag Glu											672
agg Arg 225	gct Ala	ctc Leu	cag G1n	aag Lys	tac Tyr 230	ctg Leu	cgc Arg	atc Ile	ace Thr	cgg Arg 235	cag Gln	cag Gln	aac Asn	tac Tyr	cac His 240	720
					ctg Leu											768
					ttc Phe											816
ctg Leu	caa Gln	tat Tyr 275	gac Asp	aag Lys	gac Asp	cgc Arg	tgg Trp 280	ctc Leu	tct Ser	aca Thr	cag Gln	tgg Trp 285	agg Arg	ctt Leu	gtc Val	864
Ser	gat Asp 290	gag Glu	gct Ala	gtg Val	act Thr	aat Asn 295	gga Gly	tta Leu	cgg Arg	gat Asp	99a Gly 300	att Ile	gtg Val	ttc Phe	gtc Val	912
ctt Leu 305	aag Lys	tgc Cys	ttg Leu	gac Asp	ttc Phe 310	agc Ser	ctc Leu	gta Val	Val.	aat Asn 315	gtg Val	aag Lys	aaa Lys	att Ile	cca Pro 320	960
ttc Phe	atc Ile	ata Ile	Leu	tct Ser 325	gaa Glu	gag Glu	ttc Phe	Пе	gac Asp 330	ccc Pro	aaa Lys	tct Ser	His	aaa Lys 335	ttt Phe	1008
gtc /al	ctt Leu	Arg	tta Leu 340	cag Gln	tct Ser	gag G1u	Thr	tcc Ser 345	gtt Val	taa *						1041

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<213> Homo sapiens

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<221> VARIANT

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Ser Asp Glu Ala Val Thr Asn Gly Leu Arg Asp Gly Ile Val Phe Val
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                                             300
Leu Lys Cys Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile Pro
305
                    310
                                         315
                                                             320
Phe Ile Ile Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys Phe
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Val Leu Arg Leu Gln Ser Glu Thr Ser Val
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                                     10
                                                          15
gtg gcc ggc agc ccc cga ggc cat ggg cag agc cgc gag aca acc cag
                                                                       96
Val Ala Gly Ser Pro Arg Gly His Gly Gln Ser Arg Glu Thr Thr Gln
             20
                                 25
gaa cgc agg aag aag gaa gcc aac aag gcg aca aga gcc aac cac aac
                                                                      144
Glu Arg Arg Lys Lys Glu Ala Asn Lys Ala Thr Arg Ala Asn His Asn
         35
                             40
                                                  45
cgg aga acc atg gcc gac cgc aag agg agc aaa ggc atg atc cca tcc
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Arg Arg Thr Met Ala Asp Arg Lys Arg Ser Lys Gly Met Ile Pro Ser
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tga
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<211> 64

<212> PRT

<213> Homo sapiens

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Glu	Arg	Arg 35	l Lys	Lys	Glu	. Ala	Asn 40	Lys	Ala	Thr	· Arg	45	Asn	His	Asn		
Arg ·	Arg 50	, Thr	Met	: Ala	Asp	Arg 55	Lys	Arg	Ser	Lys	Gly 60	Met	Ile	Pro	Ser		
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	<	:220> :221> :222>	CDS		1011)	·.										
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Met 1	Gly	Thr	Ser	Asp 5	Ser	His	His	Ala	Gly 10	Leu	Ser	Leu	Val	Ser 15	Arg	·	70
						gct Ala										!	96
atg Met	tca Ser	gat Asp 35	ctc Leu	tct Ser	cca Pro	gaa Glu	gag Glu 40	caa G1n	tgg Trp	agg Arg	gtc Val	gag Glu 45	cac His	gca Ala	cgc Arg	14	44
atg Met	cat His 50	gcc Ala	aag Lys	cac His	cgt Arg	ggc Gly 55	His	gaa Glu	gct Ala	atg Met	cat His 60	gct Ala	gaa Glu	atg Met	gtc Val	19	92
ctc Leu 65	atc Ile	ctc Leu	atc Ile	gca Ala	acc Thr 70	ttg Leu	gtg Val	gtg Val	gcc Ala	cag Gln 75	ctg Leu	ctc Leu	ctg Leu	gtg Val	cag Gln .80	24	10
tgg Trp	aag Lys	cag Gln	agg Arg	cac His	cca Pro	cgc Arg	tcc Ser	tac Tyr	aat Asn	atg Met	gtg Val	acc Thr	ctc Leu	ttt Phe	cag Gln	28	38

atg Met	tgg Trp	gtt Val	gtt Val 100	Pro	cto Leu	tat Tyr	ttc Phe	aca Thr	· Val	l aag Lys	ctg Leu	cad His	tgg Trp) Trp	agg Arg	336
ttc Phe	cta Leu	gtg Val 115	Пe	tgg Trp	atc Ile	ttg Leu	ttc Phe 120	Ser	gct Ala	gto Val	aca Thr	gcc Ala 125	Phe	gtt Val	acc Thr	384
		A1 a					Leu					Pro		ttg Leu		432
											Tyr			ggc Gly		480
														tta Leu 175		528
														ctt Leu		576
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tgt Cys	gca Ala 210	gac Asp	tac Tyr	atg Met	gca Ala	tct Ser 215	acc Thr	ata Ile	ggg Gly	ttc Phe	tac Tyr 220	agc Ser	gag Glu	tcg Ser	ggc Gly	672
atg Met 225	cct Pro	acc Thr	aaa Lys	cat His	ctt Leu 230	tca Ser	gac Asp	agt Ser	gtg Val	tgt Cys 235	gct Ala	gtg Val	tgt Cys	ggg Gly	cag G1n 240	720
cag Gln	atc Ile	ttt Phe	gtg Val	gac Asp 245	gtc Val	agt Ser	gaa Glu	gag Glu	999 Gly 250	atc Ile	att Ile	gag Glu	aac Asn	acg Thr 255	tat Tyr	768
		Ser					Phe							ggc Gly		816

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tag *								1011

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<213> Homo sapiens

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Phe Arg Ala Thr Arg Lys Pro Leu Val Gln Thr Thr Pro Arg Leu Val
                        135
    130
Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile
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                    150
Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu
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                165
Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu
                                185
Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met
                            200
Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly
                                            220
                        215
Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln
                                         235
                     230
Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr
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                 245
Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp
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             260
Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val
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 Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met
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 Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro
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ccc Pro	ggc Gly	acc Thr	ttc Phe 20	gtg Val	ggc Gly	acc Thr	aca Thr	gag Glu 25	ccc Pro	gcc Ala	tcc Ser	cca Pro	ccc Pro 30	ctg Leu	agc Ser	96
agc Ser	acc Thr	tca Ser 35	ccc Pro	acc Thr	act Thr	gct Ala	gcg Ala 40	gcc Ala	act Thr	atg Met	cct Pro	gtg Val 45	gtg Val	ccc Pro	tct Ser	144
gtg Val	gcc Ala 50	agc Ser	ctg Leu	gcc Ala	cct Pro	ccg Pro 55	999 Gly	gag Glu	gcc Ala	tcg Ser	ctc Leu 60	tgc Cys	ctg Leu	gaa Glu	gag Glu	192
gtg Val 65	gcc Ala	ccc Pro	cct Pro	gcc Ala	agt Ser 70	ggg Gly	acc Thr	cgc Arg	aaa Lys	gct Ala 75	cgg Arg	gtg Val	ctc Leu	tat Tyr	gac Asp 80	240
tac Tyr	gag Glu	gca Ala	gcc Ala	gac Asp 85	agc Ser	agt Ser	gag Glu	ctg Leu	gcc Ala 90	ctg Leu	ctg Leu	gct Ala	gat Asp	gag Glu 95	ctc Leu	288
atc Ile	act Thr	gtc Val	tac Tyr 100	Ser	ctg Leu	cct Pro	ggc Gly	atg Met 105	gac Asp	cct Pro	gac Asp	tgg Trp	ctc Leu 110	att Ile	ggc Gly	336
gag Glu	aga Arg	ggc Gly 115	Asn	aag Lys	aag Lys	ggc Gly	aag Lys 120	Val	cct Pro	gtc Val	acc Thr	tac Tyr 125	Leu	gaa Glu	ctg Leu	384
	agc Ser 130	*														393
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Pro	Gly	Thr	Phe 20	Val	Gly	Thr	Thr	G1u 25	Pro	Ala	Ser	Pro	Pro 30	Leu	Ser	
Ser	Thr	Ser 35	Pro	Thr	Thr	Ala	Ala 40	Ala	Thr	Met	Pro	Va1 45	Val	Pro	Ser	
Val	Ala 50	Ser	Leu	Ala	Pro	Pro 55	Gly	Glu	Ala	Ser	Leu 60	Cys	Leu	Glu	Glu	
65	Ala				70					75					80	
	Glu			85					90					95		. •
	Thr		100					105					110			
	Arg	Gly 115	Asn	Lys	Lys	Gly	Lys 120	Val	Pro	Val	Thr	Tyr 125	Leu	Glu	Leu	
Leu	Ser 130															
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		220> 221>	CDS												-	
			(1)	(1383)										
			miso	_												
			(1) n =													
		100>														
	gcc Ala															48
	ctc	a a.	000		aca	929	aaa	003		cta	000	++0	200		ast	96
	ctc Leu															90
	ctg Leu															144

cag cac ttg ctg gag cag atg gga gcc gcc tcc cgc.gtg ggc gtc ccg Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro gag cct ggc cag ctg cac ttc aac cag tgt tta act gct gaa gag atc Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile ttt tcc ctt cat ggc ttt tca aat gct acc caa ata acc agc tcc aaa Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys ttc tct gtc atc tgt cca gca gtc tta cag caa ttg aac ttt cac cca Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro tgt gag gat cgg ccc aag cac aaa aca aga cca agt cat tca gaa gtt Cys Glu Asp Arg Pro Lys His Lys Thr Arg Pro Ser His Ser Glu Val tgg gga tat gga ttc ctg tca gtg acg att att aat ctg gca tct ctc Trp Gly Tyr Gly Phe Leu Ser Val Thr Ile Ile Asn Leu Ala Ser Leu ctc gga ttg att ttg act cca ctg ata aag aaa tct tat ttc cca aag Leu Gly Leu Ile Leu Thr Pro Leu Ile Lys Lys Ser Tyr Phe Pro Lys att ttg acc ttt ttt gtg ggg ctg gct att ggg act ctt ttt tca aat Ile Leu Thr Phe Phe Val Gly Leu Ala Ile Gly Thr Leu Phe Ser Asn gca att ttc caa ctt att cca gag gca ttt gga ttt gat ccc aaa gtc Ala Ile Phe Gln Leu Ile Pro Glu Ala Phe Gly Phe Asp Pro Lys Val gac agt tat gtt gag aag gca gtt gct gtg ttt ggt gga ttt tac cta Asp Ser Tyr Val Glu Lys Ala Val Ala Val Phe Gly Gly Phe Tyr Leu ctt ttc ttt ttt gaa aga atg cta aag atg tta tta aag aca tat ggt Leu Phe Phe Phe Glu Arg Met Leu Lys Met Leu Leu Lys Thr Tyr Gly

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aaa act cat caa Lys Thr His Gln	cct aaa gca tt Pro Lys Ala Le 245	ta cct gcc atc eu Pro Ala Ile 250	aat ggt gtg aca Asn Gly Val Thr 255	tgc 768 Cys
tat gca aat cct Tyr Ala Asn Pro 260	gct gtc aca ga Ala Val Thr Gl	aa gct aat gga lu Ala Asn Gly 265	cat atc cat ttt His Ile His Phe 270	gat 816 Asp
aat gtc agt gtg Asn Val Ser Val 275	Val Ser Leu Gl	ag gat gga aaa 1n Asp Gly Lys 80	aaa gag cca agt Lys Glu Pro Ser 285	tca 864 Ser
tgt acc tgt ttg Cys Thr Cys Leu 290	aag ggg ccc aa Lys Gly Pro Ly 295	aa ctg tca gaa ys Leu Ser Glu	ata ggg acg att Ile Gly Thr Ile 300	gcc 912 Ala
tgg atg ata acg Trp Met Ile Thr 305	ctc tgc gat go Leu Cys Asp A ³ 310	cc ctc cac aat la Leu His Asn 315	ttc atc gat ggc Phe Ile Asp Gly	ctg 960 Leu 320
gcg att ggg gct Ala Ile Gly Ala	tcc tgc acc th Ser Cys Thr Le 325	tg tct ctc ctt eu Ser Leu Leu 330	cag gga ctc agt Gln Gly Leu Ser 335	act 1008 Thr
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aac ttc ctt tct Asn Phe Leu Ser 370	gca tgt tcc tg Ala Cys Ser Cy 375	gc tat gtt ggg ys Tyr Val Gly	cta gct ttt ggc Leu Ala Phe Gly 380	att 1152 Ile
ttg gtg ggc aac Leu Val Gly Asr	aat tto got co Asn Phe Ala P	ca aat att ata ro Asn Ile Ile	ttt gca ctt gct Phe Ala Leu Ala	gga 1200 Gly

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96

400 385 390 395 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 410 405 1296 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 425 420 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 1383 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu * 450 455 460 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 10 5 1 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu 45 40 Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 75 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 100 105 110

		115				His	120					125			
	130					Ser 135					140				
145					150	Pro			•	155					160
				165		Gly			170					175	
			180			Pro		185					190		
-		195				Ala	200					205			
	210					Met 215					220				
225					230	Phe				235					240
				245		Ala			250					255	
			260			Thr		265					270		
		275				Leu	280					285			
	290					Pro 295					300				
305					310	Asp				315					320
				325		Thr			330					335	
Ser	Ile	Ala	Ile 340	Leu	Cys	Glu	Glu	Phe 345	Pro	His	Glu	Leu	Gly 350	Asp	Phe
Val	Ile	Leu 355	Leu	Asn	Ala	Gly	Met 360	Ser	Thr	Arg	Gln	A1a 365	Leu	Leu	Phe
Asn	Phe 370	Leu	Ser	Ala	Cys	Ser 375	Cys	Tyr	Val	Gly	Leu 380	Ala	Phe	Gly	Пe
Leu 385	Val	Gly	Asn	Asn	Phe 390	Ala	Pro	Asn	Пе	Ile 395	Phe	Ala	Leu	Ala	Gly 400
	Met	Phe	Leu	Tyr 405	Пe	Ser	Leu	Ala	Asp 410	Met	Phe	Pro	Glu	Met 415	Asn
Asp	Met	Leu	Arg 420		Lys	Val	Thr	Gly 425		Lys	Thr	Asp	Phe 430	Thr	Phe
Phe	Met	Ile 435		Asn	Ala	Gly	Met 440		Thr	Gly	Phe	Thr 445		Пе	Leu
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							agt Ser					144
•		-	-				 cct Pro					192
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Leu Ser Arg His Met Ala His Lys Ser Glu Gln Ile Leu Lys Ala Ala
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Ser Leu Gln Val Pro Arg Pro Ser Pro Gly His His Pro Pro Ala
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Val Lys Glu Met Lys Glu Thr Gln Thr Glu Arg Asp Ile Pro Met Ser
                                        75
                    70
Asp Ser Leu Tyr Arg His Asp Ser Asp Thr Pro Ser Asp Ser Leu Asp
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Tyr Thr Gln Val Val Phe Ser Asp Pro Gly Glu Leu Lys
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gtg tcc ctc ttc ctg cag gcc tgc ttc ctc acc gcc atc aac tac ctg
                                                                       96
Val Ser Leu Phe Leu Gln Ala Cys Phe Leu Thr Ala Ile Asn Tyr Leu
                                                      30
             20
ctc agc agg cac atg gcc cac aag agt gaa cag ata ctg aaa gcg gcc
                                                                      144
Leu Ser Arg His Met Ala His Lys Ser Glu Gln Ile Leu Lys Ala Ala
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40

										cac His						192
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										ccc Pro						288
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Ser	Leu 50	Gln	Val	Pro	Arg	Pro 55	Ser	Pro	Gly	His	His 60	His	Pro	Pro	Ala	
Val 65	Lys	Glu	Met	Lys	G1u 70	Thr	Gln	Thr	G1u	Arg 75	Asp	Ile	Pro	Met	Ser 80	
	Ser			85					90					95		
	Ser		100					105					110			
	Thr	115					120					125				
	Leu 130					135					140					
145	Pro				150					155		Val	Asn	Pro	Ala 160	
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caa Gln	gcc Ala	atc Iìe	tgc Cys 20	ctg Leu	ctg Leu	cct Pro	gag Glu	agg Arg 25	gct Ala	tca Ser	gcc Ala	tac Tyr	aac Asn 30	aac Asn	cgt Arg	96
	cag Gln															144
ctg Leu	gaa Glu 50	cgc Arg	gcg Ala	gtg Val	gag Glu	ctg Leu 55	agc Ser	ggc Gly	ggc Gly	cgg Arg	ggc Gly 60	cgc Arg	gcc Ala	gcc Al·a	cgc Arg	192

										cgg Arg 75						240
_	~	_	-		-					gca Ala						288
										ccc Pro						336
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-	cgc Arg 130	tga *														393
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			Glu	5		•			10	Ala Ser				15		٠
Gln	Ala	Ile Ala	Glu Cys 20	5 Leu	Leu	Pro	Glu Gly	Arg 25	10 Ala		Ala	Tyr Ala	Asn 30	15 Asn	Arg	٠
Gln Ala	Ala Gln	Ile Ala 35 Arg	Glu Cys 20 Arg	5 Leu Arg Val	Leu Leu	Pro Gln Leu	Glu Gly 40	Arg 25 Asp Gly	10 Ala Val Gly	Ser	Ala Gly Gly	Tyr Ala 45	Asn 30 Leu	15 Asn Glu	Arg Asp	·
Gln Ala Leu Gln	Ala Gln Glu 50	Ile Ala 35 Arg	Glu Cys 20 Arg Ala	5 Leu Arg Val	Leu Leu Glu Arg	Pro Gln Leu 55	Glu Gly 40 Ser	Arg 25 Asp Gly	10 Ala Val Gly	Ser Ala Arg	Ala Gly Gly 60	Tyr Ala 45 Arg	Asn 30 Leu Ala	15 Asn Glu Ala	Arg Asp Arg Asp	·
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Gln Ala Leu Gln 65 Asp	Ala Gln Glu 50 Ser Asp	Ile Ala 35 Arg Phe Ala	Glu Cys 20 Arg Ala Val	5 Leu Arg Val Gln Arg 85	Leu Glu Arg 70 Asp	Pro Gln Leu 55 Gly Phe	Glu Gly 40 Ser Leu Glu	Arg 25 Asp Gly Leu Arg	10 Ala Val Gly Ala Ala 90	Ser Ala Arg Arg 75	Ala Gly Gly 60 Leu Arg	Tyr Ala 45 Arg Gln Leu	Asn 30 Leu Ala Gly Gly	15 Asn Glu Ala Arg Ser 95	Arg Arg Arg Asp 80 Pro	

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gag Glu 65	acc Thr	cgc Arg	cgc Arg	tgt Cys	ggc Gly 70	tcc Ser	acc Thr	tgc Cys	acc Thr	ttc Phe 75	tgg Trp	ccc Pro	tgc Cys	ttt Phe	gag Glu 80	240
ctc Leu	tgc Cys	tgt Cys	ccc Pro	gag Glu 85	tct Ser	ttt Phe	ggc Gly	ccc Pro	cag Gln 90	cag Gln	aag Lys	ttt Phe	ctt Leu	gtg Val 95	aag Lys	288
ttg Leu	agg Arg	gtt Val	ctg Leu 100	ggt Gly	atg Met	aag Lys	tct Ser	cag Gln 105	tgt Cys	cac His	tta Leu	tct Ser	ccc Pro 110	atc Ile	tcc Ser	336
	agc Ser												taa *			378

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Lys	Val	Va1 35	Ser	Gly	Arg	Ile	Ile 40	Asn	Gly	Tyr	Cys	Arg 45	G1y	Asp	Trp	
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		-				-	-						aac Asn			240
-				_	-			-	-				cag Gln			288
-		-	-										tgg Trp 110			336
~				-	•			-	-				gag Glu		_	384
_	_			-	_								cag Gln			432
													gcc Ala			480
													cag Gln			528
~~~	_				-	_	_	_		-			ccc Pro 190		_	576
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441

gac ttc tag

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Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu Ala Asp Trp Val Cys
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Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Ala Leu Asp Tyr Glu
Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
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Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
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										atg Met						3	192
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	gtc Val														336
	gaa Glu														384
	cta Leu 130														432
	agg Arg			-	-										480
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	agc Ser		-		-	-								-	576
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-					-							_	-	gaa Glu	-	384
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						gcg Ala									-		864
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			420					425			His		430		
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465					470	-				475	Phe		•		480
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Arg	G1n 530	Arg	Ala	Glu	Ala	Arg 535	Glu	Arg	Lys	Glu	Lys 540	Glu	Ile	Gln	Trp
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Thr		Lys	Arg	Lys	Ala		Ser	Glu	Arg	Arg		Met	Gly	Tyr	Ser		
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	gtc Val	_	-						_		_	_				336
-	gtc Val	-	-	-	_		_		_							384
	att Ile 130				-					-			-		_	432
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Tyr 65	Lys	Cys	Ser	Asp	Gly 70	Ser	Lys	Pro	Phe	Pro 75	Arg	Tyr	Gly	Tyr	Lys 80		
Pro	Ser	Pro	Pro	Asn 85	Gly	Cys	Gly	Ser	Pro 90	Leu	Phe	Gly	Val	His 95	Leu		
Asn	He	Gly	Ile 100	Pro	Ser	Leu	Thr	Lys 105	Cys	Cys	Asn	Gln	His 110	Asp	Arg		
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PCT/US00/29052

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Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
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Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
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											atc Ile				816
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													gtg Val		576
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	cag Gln													768
	gtg Val													816
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	cac His 290													912
	ctc Leu	_	-	-	-	-								960
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Gln	His 290	Gln	Val	Trp	Asp	Val 295	Ala	Phe	G1u	G1u	Thr 300	Gln	Gly	Leu	Trp	
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Gly	Asp	Gln	Trp	G1n 325	Ser	Val	Pro	Glu	Ser 330	Thr	Val	Leu	Lys	Lys 335	Val	
Ser	Gly	Val	Leu 340	Arg	Gly	Asn	Trp	A1a 345	Met	Leu	Glu	Gly	Ser 350	Ala	Gly	
	•	355					360			Ala		365	·			
Thr	Şer 370	Tyr	Leu	Lys	Lys	Lys 375	Glu	Glu	Arg	Leu	G1n 380	Gln	Gln	Leu	Glu	
Lys 385	Lys	Gln	Arg	Arg	Arg 390	Ser	Pro	Pro	Pro	G1y 395	Pro	Asp	Gly	His	Ala 400	
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										ata Ile						144
										act Thr						192
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							tac Tyr 120									384
							gac Asp									432
			-	_		-	aaa Lys		-				-		-	480
-			_		_	-	tgc Cys			-		-	-	-	-	528
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Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
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Gln Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
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Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
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Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
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Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
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Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
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	tgc Cys															1	144
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				-	-	-				atg Met	192
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His	Glu	Asn 35	Lys	Tyr	G1y	Lys	Gly 40	Ile	Tyr	Phe	Ala	Lys 45	Asp	Ala	Ile	
Tyr	Ser 50	His	Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60	Val	Val	Met	Phe	
Va1 65	Ala	Gln	Val	Leu	Va1 70	Gly	Lys	Phe	Thr	G1u 75	Gly	Asn	He	Thr	Tyr 80	
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	Val	Asp	Thr	Arg	Ser 95	Asn	
Pro	Ser	Val	Phe 100	Val	Ile	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110	<u>G</u> In	Tyr	
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	aaa Lys 50		_												_	192

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									aaa Lys	-		-			288
									gag Glu				-		336
									tca Ser		-				384
	-		_						tca Ser 140			-		· .	432
	_					_		 -	tca Ser		-				480
						-			cta Leu				-	!	528
									cct Pro					!	576
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			-	-						cag Gln					1056
-	-	_	-	-	-	_	-	-		ctc Leu		_			1104
		-					_		-	ttt Phe		-		_	1152
-	-				-			_		cat His 395	-	 -		_	1200
										cga Arg					1248

	•	_			-		ttg Leu 425		-		•			_	1296
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		-	-				ggt Gly		-	-		-		_	1440
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							gtg Val								1584
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			-				tgg Trp				-			-	1680
ggc Gly															1728
cag Gln						Lys									1776

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Leu Asp Gly Ser Asn Lys Ser His Lys Val Lys Ser Ser Gln Gln Pro 115 120 125 Ala Ala Ser Thr Gln Leu Pro Thr Thr Pro Ser Ser Asn Pro Ser Gly 130 135 140

Gln Leu Gln Lys Ile Arg Asp Leu Ile Ala Ile Glu Arg Ser Ser Arg

90 ·

85

Leu Asn Gln His Thr Arg Asn Arg Gln Gly Gln Ser Ser Asp Pro Pro 145 150 155 160

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Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys	Glu	G1u 240
Phe	Phe	His	Trp	Va1 245	Asn	Asn	۷a٦	Leu	Cys 250		Lys	Cys	Gly	Gly 255	Gln
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305					Gly 310		•			315				Ť	320
				325	Glu				330					335	
Val	Trp	Thr	G1u 340	Val	Tyr	Ser	Pro	Ser 345	Gln	Gln	Arg	Trp	Leu 350	His	Cys
Asp	Ala	Cys 355	Glu	Asp	Val	Cys	Asp 360	Lys	Pro	Leu	Leu	Tyr 365	Glu	Ile	Gly
Trp	G1y 370	Lys	Lys	Leu	Ser	Tyr 375	Val	Ile	Ala	Phe	Ser 380	Lys	Asp	Glu	Val
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Arg	Arg	Thr	Lys	Val 405	Lys	Glu	Ala	Leu	Leu 410	Arg	Asp	Thr	Ile	Asn 415	Gly
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Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	Пe	Ser 460	Gly	Ser	Val	Ala
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Phe	He	Pro	Cys	G1u 485	Asn	Glu	Lys	Ile	Ser 490	Lys	Gln	Leu	Нis	Leu 495	Cys
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Thr	Пe	Ser 515	Gly	Trp	Glu	Asn	G1 <i>y</i> 520	Val	Trp	Lys	Met	G1u 525	Ser	Пe	Phe	
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Gly 545	Ser	Ser	Phe	Ala	Tyr 550	Ile	Ser	Tṛp	Lys	Phe 555	Glu	Cys	Gly	Ser	Val 560	
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	cct Pro															144
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				gct Ala							2	288
				atg Met							3	336
				aca Thr				-	-		3	384
				act Thr 135								132
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Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
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Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
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Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
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Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
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					aag Lys				384
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taa	Pro	cac					200					205		Lys		
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					gtc Val											768
					tgc Cys		-			-						816
					999 Gly			-				-	-		•	864
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	ata Ile	_		_			-					288
	gtc Val											336
	ttg Leu											384
	ttc Phe 130											432

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atc Ile	tcc Ser	cta Leu	gag Glu	gtg Val 165	Ile	ttc Phe	cgg Arg	gac Asp	cac His 170	Ile	gtg Val	ctg Leu	gaa Glu	ctt Leu 175	ttc Phe	528	
cga Arg	acc Thr	agt Ser	ctc Leu 180	atc Ile	att Ile	ctt Leu	cag G1n	gga Gly 185	acc Thr	tgg Trp	ttc Phe	tgg Trp	cag Gln 190	att Ile	999 Gly	576	
ttt Phe	gtg Val	ctg Leu 195	ttc Phe	cca Pro	cct Pro	ttt Phe	gga Gly 200	aca Thr	ccc Pro	gaa Glu	tgg Trp	gac Asp 205	cag Gln	aag Lys	gat Asp	624	
gat Asp	gcc Ala 210	aac Asn	ctc Leu	atg Met	ttc Phe	atc Ile 215	acc Thr	atg Met	tgc Cys	ttc Phe	tgc Cys 220	tgg Trp	cac His	tac Tyr	ctg Leu	672	
gct Ala 225	gcc Ala	ctc Leu	agc Ser	att Ile	gtg Val 230	gcc Ala	gtc Val	aac Asn	tat Tyr	tct Ser 235	ctt Leu	gtt Val	tac Tyr	tgc Cys	ctt Leu 240	720	
ttg Leu	act Thr	cgg Arg	atg Met	aag Lys 245	aga Arg	cac His	gga Gly	Arg	99a G1y 250	gaa Glu	atc Ile	att Ile	gga Gly	att Ile 255	cag G1n	768	
aag Lys	ctg Leu	aat Asn	tca Ser 260	gat Asp	gac Asp	act Thr	Tyr	cag Gln 265	acc Thr	gcc Ala	ctc Leu	Leu	agt Ser 270	ggc Gly	tca Ser	816	
gat Asp	Glu		tga *													828	
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Thr Arg Lys Asn Ser Pro Leu His Tyr Tyr Gln Arg Leu Glu Ile Val
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Glu Ala Ala Ile Arg Thr Leu Phe Ser Val Thr Gly Ile Leu Ala Glu
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Gln Phe Val Pro Asp Gly Pro His Leu His Leu Tyr His Glu Asn His
Trp Ile Lys Leu Met Asn Trp Gln His Ser Thr Met Tyr Leu Phe Phe
                                    90
Ala Val Ser Gly Ile Val Asp Met Leu Thr Tyr Leu Val Ser His Val
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Pro Leu Gly Val Asp Arg Leu Val Met Ala Val Ala Val Phe Met Glu
                            120
Gly Phe Leu Phe Tyr Tyr His Val His Asn Arg Pro Pro Leu Asp Gln
                        135
                                            140
His Ile His Ser Leu Leu Leu Tyr Ala Leu Phe Gly Gly Cys Val Ser
                                         155
Ile Ser Leu Glu Val Ile Phe Arg Asp His Ile Val Leu Glu Leu Phe
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                                    170
Arg Thr Ser Leu Ile Ile Leu Gln Gly Thr Trp Phe Trp Gln Ile Gly
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Phe Val Leu Phe Pro Pro Phe Gly Thr Pro Glu Trp Asp Gln Lys Asp
                            200
Asp Ala Asn Leu Met Phe Ile Thr Met Cys Phe Cys Trp His Tyr Leu
                        215
                                            220
Ala Ala Leu Ser Ile Val Ala Val Asn Tyr Ser Leu Val Tyr Cys Leu
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Leu Thr Arg Met Lys Arg His Gly Arg Gly Glu Ile Ile Gly Ile Gln
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						gcc Ala							240
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						ggt Gly				_		-	336
-				_		gcc Ala	-				-		384
						gtg Val							432
			Пe			ctc Leu							480
						ctt Leu							528

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									tat Tyr						624
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_	-			-			 		tca Ser 235		-				720
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<213> Homo sapiens

<400> 120

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Asn	Gly 50	Gly	Ala	Ser	Glu	Ala .55	Gly	Glu	Asp	Arg	Glu 60	Ala	Pro	Gly	Lys
Arg 65	Arg	Arg	Leu	Gly	Phe 70	Leu	Ala	Thr	Ala	Trp 75	Leu	Thr	Phe	Tyr	Asp 80
Ile	Ala	Met	Thr	Ala 85	Gly	Trp	Leu	Val	Leu 90	Ala	Ile	Ala	Met	Val 95	Arg
Phe	Tyr	Met	Glu 100	Lys	Gly	Thr	His	Arg 105	Gly	Leu	Tyr	Lys	Ser 110	Пе	Gln
Lys	Thr	Leu 115	Lys	Phe	Phe	G1n	Thr 120	Phe	Ala	Leu	Leu	G1u 125	Ile	Val	His
Cys	Leu 130	He	Gly	Ile	Val	Pro 135	Thr	Ser	Val	Ile	Val 140	Thr	Gly	Val	Gln
Val 145	Ser	Ser	Arg	Ile	Phe 150	Met	Val	Trp	Leu	Ile 155	Thr	His	Ser	He	Lys 160
Pro	Ile	Gln	Asn	G1u 165	Glu	Ser	Val	Val	Leu 170	Phe	Leu	Val	Ala	Trp 175	Thr
Val	Thr	Glu	Ile 180	Thr	Arg	Tyr	Ser	Phe 185	Tyr	Thr	Phe	Ser	Leu 190	Leu	Asp
His	Leu	Pro 195	Tyr	Phe	Ile	Lys	Trp 200	Ala	Arg	Tyr	Asn	Phe 205	Phe	Ile	Пe
Leu	Tyr 210	Pro	Val	Gly	Val.	Ala 215	Gly	Glu	Leu	Leu	Thr 220	Ile	Tyr	Ala	Ala
Leu 225	Pro	His	Val	Lys	Lys 230	Thr	Gly	Met	Phe	Ser 235	Ile	Arg	Leu	Pro	Asn 240
Lys	Tyr	Asn	Val	Ser 245	Phe	Asp	Tyr	Tyr	Tyr 250	Phe	Leu	Leu	Пe	Thr 255	Met
Ala	Ser	Tyr	Ile 260	Pro	Leu	Phe	Pro	G1n 265	Leu	Tyr	Phe	His	Met 270	Leu	Arg
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						ctg Leu										144
						tcc Ser 55				tag *						177
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Thr	Пe	Lys		Ser	Ser	Gln	Thr	_	Glu	Trp	Gln	Asn		Ala	Ile	
Met	Thr	G1u 35	20 Glu	Pro	Glu	Leu	Ser 40	25 Pro	Ala	Tyr	Leu	Ile 45	30 Ser	Glu	Ala	
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			cag Gln													144
			gtt Val		_			-		-	-		-	_	-	192
			tgg Trp			Met										240
			ccc Pro													288
			tgt Cys 100							-						336
			atg Met													384
Leu			tgg Trp							_				_		432
ctg Leu 145	tgt Cys	gtt Val	acc Thr	aat Asn	gct Ala 150	atg Met	cga Arg	gaa Glu	gac Asp	ctg Leu 155	gcg Ala	gat Asp	aac Asn	tgg Trp	cac His 160	480
			gtg Val													528
aca Thr	cct Pro	ctg Leu	gac Asp	ctg Leu	cag G1n	cac His	cgg Arg	ctc Leu	ttc Phe	atg Met	aag Lys	ctg Leu	ggc Gly	agc Ser	atg Met	576

			180					185					190			
					-					gag Glu			_	_		_. 624
				-				_		agc Ser		_		-	-	672
L										agc Ser 235						720
-						_	-		-	ŧta Leu	-	_		_		768
	_		-							ctc Leu	-	-				816
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										tgg Trp						912
T										ggt Gly 315					-	960
										gtg Val						1008
		Leu								aag Lys						1056
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Asp Glu Asp Phe Ser Ile Leu Leu Ala Ala Leu Glu Lys Phe Glu Gln
                245
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Leu Thr Leu Asp Gly His Asn Leu Pro Ser Leu Val Cys Val Ile Thr
                                265
Gly Lys Gly Pro Leu Arg Glu Tyr Tyr Ser Arg Leu Ile His Gln Lys
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His Phe Gln His Ile Gln Val Cys Thr Pro Trp Leu Glu Ala Glu Asp
                        295
                                            300
Tyr Pro Leu Leu Gly Ser Ala Asp Leu Gly Val Cys Leu His Thr
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                                        315
Ser Ser Ser Gly Leu Asp Leu Pro Met Lys Val Val Asp Met Phe Gly
                325
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Cys Cys Leu Pro Val Cys Ala Val Asn Phe Lys Cys Leu His Glu Leu
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Val Lys His Glu Glu Asn Gly Leu Val Phe Glu Asp Ser Glu Glu Leu
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Ala Ala Gln Leu Gln Met Leu Phe Ser Asn Phe Pro Asp Leu Arg Ala
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Ser
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                                                         15
ggc ggc ggc ggc ggc ggc gcc ggc ggc tgc ggg gcg ctg act gcc ggc
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Gly Gly Gly Gly Gly Ala Gly Gly Cys Gly Ala Leu Thr Ala Gly
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							-		cta Leu 90			-	-	-	288
									gac Asp						336
-		_		_		-			att Ile		_	_			384
				-	_	-	_	-	tca Ser			-			432
					-	_	-		aat Asn	-				_	480
									cat His 170			_		-	528
			-						cta Leu						576
			_			_	-		gag Glu					-	624

	•	195					200					205				
				-	_	_		_		_	-	cga Arg				672
												tgg Trp				720
												ctt Leu				768
									-			ttc Phe				816
	-	-	_	-	•		•			-	•	aca Thr 285	_	-	~	864
	-		•	_	_	-	_	_				cta Leu				912
		-				_		-				tac Tyr				960
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Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45	G1n	His	His
Arg	Thr 50	Val	His	Gln	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	Val
Tyr 65	Cys	Ser	Thr	Val	Va1 70	Pro	Ser	Asp	Asp	Val 75	Thr	Val	Val	Tyr	G1n 80
Asn	Gly	Leu	Pro	Va1 85	Пe	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	G1u 95	Arg
Cys	Gln	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
Arg	Gln	Leu 115	Gln	Glu	Glu	Asp	Arg 120	Gly	Ile	Asp	Arg	Val 125	Ala	Ile	Tyr
Ser	Pro 130	Asp	Gly	Val	Arg	Val 135	Ala	Ala	Ser	Thr	Gly 140	Ile	Asp	Leu	Leu
Leu 145	Leu	Asp	Asp	Phe	Lys 150	Leu	۷a٦	Пe	Asn	Asp 155	Leu	Thr	Tyr	His	Val 160
		•	Lys	165					170					175	
			Lys 180					185					190		
Glu	Gln	His 195	Gln	Leu	Asn	Lys	G1u 200	Arg	Glu	Leu	Ile	G1u 205	Arg	Leu	G1u
Asp	Leu 210	Lys	Glu	Gln	Leu	Ala 215	Pro	Leu	Glu	Lys	Val 220	Arg	Ile	G1u	Ile
Ser 225	Arg	Lys	Ala	Glu	Lys 230	Arg	Thr	Thr	Leu	Va1 235	Leu	Trp	Gly	Gly	Leu 240
Ala	Tyr	Met	Ala	Thr 245	Gln	Phe	Gly	Пe	Leu 250	Ala	Arg	Leu	Thr	Trp 255	Trp
			Trp 260	-				265					270		-
G1y	Ser	A1a 275	Met	Ala	Met	Tyr	Ala 280	Tyr	Phe	Val	Met	Thr 285	Arg ·	Gln	G1u
Tyr	Va1 290	Tyr	Pro	Glu	Ala	Arg 295	Asp	Arg	Gln	Tyr	Leu 300	Leu	Phe	Phe	His
Lys 305	Gly	Ala	Lys	Lys	Ser 310	Arg	Phe	Asp	Leu	G1u 315	Lys	Tyr	Asn	Gln	Leu 320
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						aga Arg 55										1	192
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ctt _eu	cga Arg	gac Asp	cac His	atg Met 85	aat Asn	aca Thr	cac His	acc Thr	aac Asn 90	aga Arg	cgc Arg	cct Pro	tac Tyr	agt Ser 95	tgt Cys	2	288
:99 \rg	att Ile	tgt Cys	cgc Arg 100	aag Lys	tcc Ser	tat Tyr	gta Val	cgt Arg 105	cct Pro	ggc Gly	agc Ser	ctg Leu	agc Ser 110	aca Thr	cac His	3	36
itg	aaa	ctt	cat	cat	ggt	gag	aac	cgt	ctg	aag	aaa	ctc	atg	tgt	tgt	3	84

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															ccc Pro	agt Ser 160	480
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															gaa Glu		576
															aaa Lys		624
															ttt Phe		672
															gaa Glu		720
															cac His 255		768
			Asp		Lys										aag Lys		816
	cat His	Ser	tcc Ser 275	tcc Ser	gag G1u	gaa Glu	Ser	cat His 280	gca Ala	tgt Cys	cca Pro	aga Arg	ctg Leu 285	aaa Lys	agg Arg	cag Gln	864
	ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

Leu	His 290	Leu	His	Gln	Asn	Gly 295	Val	Glu	Met	Leu	Met 300	Glu	Asn	Glu	Gly		
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					acg Thr											1008	
					gag Glu											1056	
					cat His											1104	
att Ile	tta Leu 370	aat Asn	acg Thr	gtc Val	tcc Ser	aac Asn 375	cag Gln	gga Gly	gtg Val	atc Ile	gaa Glu 380	ctt Leu	tcc Ser	agt Ser	gaa Glu	1152	
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Leu	ınr	rro	Lys	ıyr	Leu	ч	Lys	Lys	GIN	ASP	Asn	ser	5er	5er	rro		

		35					40					45			
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Trp 65	His	Arg	Cys	His	Val 70	Cys	Asn	His	His	Phe	Gln	Phe	Lys	Gln	His 80
Leu	Arg	Asp	His	Met 85	Asn	Thr	His	Thr	Asri 90	Arg	Arg	Pro	Tyr	Ser 95	Cys
Arg	He	Cys	Arg 100	Lys	Ser	Tyr	Val	Arg 105		Gly	Ser	Leu	Ser 110	Thr	His
Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys.	Lys	Leu 125	Met	·Cys	Cys
Glu	Phe 130	Cys	Ala	Lys	Val	Phe 135	Gly	His	Пe	Arg	Val 140	Tyr	Phe	Gly	His
Leu 145	Lys	Glu	Val	His	Arg 150	Val	Val	Ile	Ser	Thr 155	Glu	Pro	Ala	Pro	Ser 160
G1u	Leu	Gln	Pro	Gly 165	Asp	Пe	Pro	Lys	Asn 170	Arg	Asp	Met	Ser	Val 175	Arg
Gly	Met	Glu	Gly 180	Ser	Leu	Glu	Arg	Glu 185	Asn	Lys	Ser	Asn	Leu 190	Glu	Glu
Asp	Phe	Leu 195	Leu	Asn	G1n	Ala	Asp 200	Glu	Val	Lys	Leu	G1n 205	Ile	Lys	Cys
Gly	Xaa 210	Cys	Gln	Пe	Thr	Ala 215	Gln	Ser	Phe	Ala	G1u 220	He	Lys	Phe	His
Leu 225	Leu	Asp	Val	His	Gly 230	Glu	<b>G</b> 1u	Ile	Glu	Gly 235	Arg	Leu	Gln	Glu	Gly 240
Thr	Phe	Pro	Gly	Ser 245	Lys	Gly	Thr	Gln	G1u 250	Glu	Leu	Val	Gln	His 255	Ala
Ser	Pro	Asp	Trp 260	Lys	Arg	His	Pro	Glu 265	Arg	Gly	Lys	Pro	G1u 270	Lys	Val
His	Ser	Ser 275	Ser	Glu	Glu	Ser	His 280	Ala	Cys	Pro	Arg	Leu 285	Lys	Arg	Gln
Leu	His 290	Leu	His	Gln	Asn	Gly 295	Val	Glu	Met	Leu	Met 300	G1u	Asn	Glu	Gly
Pro 305	G1n	Ser	Gly	Thr	Asn 310	Lys	Pro	Arg	Glu	Thr 315	Cys	Gln	Gly	Pro	Glu 320
Cys	Pro	Gly	Leu	His 325	Thr	Phe	Leu	Leu	Trp 330	Ser	His	Ser	Gly	Phe 335	Asn
Cys	Leu	Leu	Cys 340	Ala	Glu	Met	Leu	Gly 345	Arg	Lys	Glu	Asp	Leu 350	Leu	His
His	Trp	Lys 355	His	Gln	His	Asn	Cys 360	Glu	Asp	Pro	Ser	Lys 365	Leu	Trp	Ala
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	Pro						gaa G1u			-						. 4	180
							ctg Leu									5	528
							aac Asn		Asp							5	576
	-						gtc Val 200									6	524
							tgt Cys	-				_	_			• 6	572
		-				_	tat Tyr	_	-		-	_				7	720
-					-	-	999 Gly		-							7	'68
							gct Ala									8	316
							gtc Val 280						-	-		8	364

											tca Ser 300			_	_	912
											cag Gln					960
		_			_	-					aac Asn	_	-		-	1008
				_	•						tat Tyr	-			_	1056
											gct Ala					1104
	_			-	-		_	_			acg Thr 380	_	-			1152
-								-			gaa Glu					1200
		_		-						-	atc Ile					1248
											cag Gln					1296
											aag Lys					1344
		-	_		_	-			-	-	tat Tyr 460	_	-			1392

	His			-	aag Lys 470				_				-			1440
					acc Thr		_							-		1488
	_	-			agg Arg		-		-		_	_				1536
				_	agc Ser		-	-		-		_				1584
				•	gtt Val		_					_	-		-	1632
-			_		agt Ser 550			-		-	-	_				1680
					ggt Gly		_					_				1728
		-			tta Leu					_				-	-	1776
		_			agc Ser	_		_		-		-			_	1824
					act Thr											1872
					gaa Glu 630			-							-	1920

			att Ile													1968
-		_	gaa G1u 660	-												2016
cct Pro	tga *			,				`								2022
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1	Lys	Lys	Asp His	5				Gly	10					15		
1 Ala	Lys Cys	Lys Pro	Asp	5 Met	Ala	Thr	Cys	Gly 25	10 Asn	Val	Leu	Phe	G1u 30	15 Gly	Arg	
1 Ala Thr	Lys Cys Val	Lys Pro Gln 35	Asp His 20	5 Met Gly	Ala Lys	Thr Leu	Cys Cys 40	Gly 25 Cys	10 Asn Thr	Val Gly	Leu Val	Phe Glu 45	Glu 30 Thr	15 Gly Glu	Arg Asp	
1 Ala Thr Asp	Lys Cys Val Glu 50	Lys Pro Gln 35 Asp	Asp His 20 Leu	5 Met Gly Glu	Ala Lys Ser	Thr Leu Asn 55	Cys Cys 40 Ser	Gly 25 Cys Ser	10 Asn Thr Val	Val Gly Glu	Leu Val Gln 60	Phe Glu 45 Ala	Glu 30 Thr	15 Gly Glu Val	Arg Asp Glu	
1 Ala Thr Asp Val 65	Lys Cys Val Glu 50 Pro	Lys Pro Gln 35 Asp	Asp His 20 Leu Thr	5 Met Gly Glu Pro	Ala Lys Ser Thr 70	Thr Leu Asn 55 Leu	Cys Cys 40 Ser His	Gly 25 Cys Ser Asp	10 Asn Thr Val Pro	Val Gly Glu Asp 75	Leu Val Gln 60 Leu	Phe Glu 45 Ala Tyr	Glu 30 Thr Ser	15 Gly Glu Val Glu	Arg Asp Glu Ile 80	
1 Ala Thr Asp Val 65 Val	Lys Cys Val Glu 50 Pro Lys	Lys Pro Gln 35 Asp Asp	Asp His 20 Leu Thr Gly	5 Met Gly Glu Pro Lys 85	Ala Lys Ser Thr 70 Ser	Thr Leu Asn 55 Leu Val	Cys Cys 40 Ser His	Gly 25 Cys Ser Asp Glu	10 Asn Thr Val Pro Tyr 90	Val Gly Glu Asp 75 Ser	Leu Val Gln 60 Leu Glu	Phe Glu 45 Ala Tyr	Glu 30 Thr Ser Ile Ala	15 Gly Glu Val Glu Tyr 95	Arg Asp Glu Ile 80 Pro	
1 Ala Thr Asp Val 65 Val Asp	Lys Cys Val Glu 50 Pro Lys	Lys Pro Gln 35 Asp Asp Asn	Asp His 20 Leu Thr Gly Thr	5 Met Gly Glu Pro Lys 85 His	Ala Lys Ser Thr 70 Ser	Thr Leu Asn 55 Leu Val Pro	Cys Cys 40 Ser His Pro	Gly 25 Cys Ser Asp Glu Pro 105	10 Asn Thr Val Pro Tyr 90 Phe	Val Gly Glu Asp 75 Ser Lys	Leu Val Gln 60 Leu Glu Glu	Phe Glu 45 Ala Tyr Val	Glu 30 Thr Ser Ile Ala Ile 110	15 Gly Glu Val Glu Tyr 95 Leu	Arg Asp Glu Ile 80 Pro Glu	
1 Ala Thr Asp Val 65 Val Asp	Lys Cys Val Glu 50 Pro Lys Tyr	Lys Pro Gln 35 Asp Asp Asn Phe Tyr 115	Asp His 20 Leu Thr Gly Thr Gly 100	5 Met Gly Glu Pro Lys 85 His	Ala Lys Ser Thr 70 Ser Ile Gln	Thr Leu Asn 55 Leu Val Pro	Cys 40 Ser His Pro Pro	Gly 25 Cys Ser Asp Glu Pro 105 Lys	10 Asn Thr Val Pro Tyr 90 Phe	Val Gly Glu Asp 75 Ser Lys	Leu Val Gln 60 Leu Glu Glu Gln	Phe Glu 45 Ala Tyr Val Pro Asp 125	Glu 30 Thr Ser Ile Ala Ile 110 Ile	15 Gly Glu Val Glu Tyr 95 Leu Glu	Arg Asp Glu Ile 80 Pro Glu Arg	

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Asn	Glu	Tyr	Asp 180	Leu		Leu	Asn	Ser 185	Asp	Пe	Asn	Ser	Asn 190		
His	Gl'n	Trp 195		Tyr	Phe	Glu	Val 200		Gly	Met	Arg	Pro 205	-	Val	Ala
Tyr	Arg 210	Phe	Asn	Ile	Ile	Asn 215	_	Glu	Lys	Ser	Asn 220	Ser	Gln	Phe	Asr
Tyr 225	Gly	Met	Gln	Pro	Leu 230	Met	Tyr	Ser	Val	G1n 235		Ala	Leu	Asn	A1a 240
Arg	Pro	Trp	Trp	Ile 245		Met	Gly	Thr	Asp 250	Пe	Cys	Tyr	Tyr	Lys 255	Asr
His	Phe	Ser	Arg 260	Ser	Ser	Val	Ala	A1 a 265	Gly	Gly	Gln	Lys	G1y 270	Lys	Ser
		275					280		Phe			285	·	•	
Cys	Tyr 290	Phe	Ala	Tyr	His	Tyr 295	Pro	Tyr	Thr	Tyr	Ser 300	Thr	Leu	Gln	Met
His 305	Leu	Gln	Lys	Leu	GTu 310	Ser	Ala	His	Asn	Pro 315	Gln	G1n	He	Tyr	Phe 320
Arg	Lys	Asp	۷a·۱	Leu 325	Cys	Glu	Thr	Leu	Ser 330	Gly	Asn	Ser	Cys	Pro 335	Leu
Val	Thr	He	Thr 340	Ala	Met	Pro	Glu	Ser 345	Asn	Tyr	Tyr	Glu	His 350	Ile	Cys
His	Phe	Arg 355	Asn	Arg	Pro	Tyr	Va1 360	Phe	Leu	Ser	Ala	Arg 365	Val	His	Pro
	370					375			Lys	-	380				
385					390				Leu	395			-		400
Lys	Ile	Val	Pro	Met 405	Leu	Asn	Pro	Asp	Gly 410	Val	Пе	Asn	Gly	Asn 415	His
			420				-	425	Asn				430		
Ser	Pro	Asp 435	Leu	His	Pro	Thr	Ile 440	Tyr	His	Ala	Lys	Gly 445	Leu	Leu	Gln
Tyr	Leu 450	Ala	Ala	Val	Lys	Arg 455	Leu	Pro	Leu	Val	Tyr 460	Cys	Asp	Tyr	His
Gly 465	His	Ser	Arg	Lys	Lys 470	Asn	Val	Phe	Met	Tyr 475	Gly	Cys	Ser	Ile	Lys 480
Glu	Thr	Val	Trp	His 485	Thr	Asn	Asp	Asn	A1a 490	Thr	Ser	Cys	Asp	Val 495	Val
Glu	Asp	Thr	G1y 500	Tyr	Arg	Thr		Pro 505	Lys	Пe	Leu	Ser	His 510	Ile	A1 a

Pro	Аlа	Phe 515	Cys	Met	Ser	Ser	Cys 520	Ser	Phe	Val	Val	G1u 525	Lys	Ser	Lys	
Glu	Ser 530	Thr	Ala	Arg	Val	Val 535	Val	Trp	Arg	Glu	Ile 540	Gly	Val	Gln	Arg	
Ser 545	Tyr	Thr	Met	Glu	Ser 550	Thr	Leu	Cys	Gly	Cys 555	Asp	Gln	Gly	Lys	Tyr 560	
Lys	G1y	Leu	Gln	Ile 565	Gly	Thr	Arg	Glu	Leu 570	Glu	Glu	Met	Gly	A1a 575	Lys	
Phe	Cys	Val	Gly 580	Leu	Leu	Arg	Leu	Lys 585	Arg	Leu	Thr	Ser	Pro 590	Leu	Glu	
Tyr	Asn	Leu 595	Pro	Ser	Ser	Leu	Leu 600	Asp	Phe	Glu	Asn	Asp 605	Leu	Ile	Glu	
	610		-			615	Pro				620		•		·	
625					630		Val			635					640	
				645			Glu		650					655,		
	Gln	Glu	G1u 660	Val	Leu	Ser	Asp	Ser 665	Glu	Leu	Ser	Arg	Thr 670	Tyr	Leu	
Pro																
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							Leu									40
_			_	_			ttc Phe									96
		-					agc Ser 40									144

						ctg Leu 55										192
						gtc Val		-						-		240
						acc Thr										288
						ttt Phe										336
						cac His		Gly		_		tga *	4			375
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	Tyr	Ser	Leu 20		۷a٦	Ala	Phe	Leu 25		Ile	Ser	Thr	Thr 30		Gly	
Gly	Phe	Cys 35		Ser	Gly	Phe	Ser 40		Asn	His	Leu	Asp 45		Ala	Pro	
Ser	Tyr 50		Gly	Пе	Leu	Leu 55		Пе	Thr	Asn	Thr 60		Ala	Thr	Ile	
		Met	Val	Gly		Val	Ile	Ala	Lys			Thr	Pro	Asp		
65 Thr	Val	Gly	Glu		70 G1n	Thr	۷a٦	Phe		75 Ile	Ala	Ala	Ala		80 Asn	
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Asn													T T O			

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	acc Thr															240
	aag Lys															288
	ggc Gly													Phe		336
cgt	ccc	cct	cga	tgt	tcc	cac	tgc	agt	gtc	tgt	gac	aac	tgt	gtg	gag	384

Arg	Pro	Pro 115	Arg	Cys	-Ser	His	Cys 120	Ser	Val	Cys	Asp	Asn 125	Cys	Val	Glu	
											tgt Cys 140					432
		-									ctg Leu		-			480
											ctc Leu					528
										-	gca Ala	-	_	-		576
							-	_			acg Thr				-	624
											cag Gln 220					672
											tgc Cys	-			-	720
					_						tat Tyr	_		-		768
											ttc Phe					816
	Ser					Thr					gat Asp					864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	912

Glv	Glu	Leu	Ara	Ara	Thr	Lvs	Ser	Lvs	Gly	Ser	Leu	Glu	Πρ	Thr	Glu		
	290	200	7 H 9	711 9	••••	295	501		u.,		300	414	110		Giu		
	Gln								cct								960
						_			ctc Leu 330		_	_					1008
									ccc Pro								1056
				-			-	_	agt Ser	-		-	-	_	_		1104
									ggg Gly								1152
					-	-			ccc Pro			_					1200
					-				cct Pro 410					_			1248
									cgc Arg			_		_			1296
						Glu			cag G1n								1344
Glu					Thr				agc Ser							•	1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	<i>.</i>	1440

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 470 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu * 485 490 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr Val Pro Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro 40 Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 75 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile 90 Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr 105 Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asn Cys Val Glu 120 Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 150 155 Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 170 Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val

180 185 190
Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

		195					200					205			
Val	Leu 210	Val	Ala	Arg	Gly	Arg 215	Thr	Thr	Asn	Glu	G1n 220	Val	Thr	Gly	Lys
Phe 225	Arg	Gly	Gly	Val	Asn 230	Pro	Phe	Thr	Asn	G1y 235	Cys	Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245	Ser	Ser	Pro	Ala	Pro 250	Arg	Tyr	Leu	Gly	Arg 255	Pro
Lys	Lys	Glu	Lys 260	Thr	Ile	Val	Ile	Arg 265	Pro	Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	Ile	Thr	Va1 280	Lys	Пe	Met	Asp	Asn 285	Gly	Ile	G1n
Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Ile	Thr	Glu
Ser 305	Gln	Ser	Ala	Asp	Ala 310	Glu	Pro	Pro	Pro	Pro 315	Pro	Lys	Pro	Asp	Leu 320
Ser	Arg	Tyr	Thr	Gly 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	G1u
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Ser	Ser 360	Ser	Ser	Thr	Ser	A1a 365	Ala	Met	Pro
His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	Ile	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	G1u	Pro 400
Ser	Leu	G1u	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
His	Phe	Asp	Pro 420	Leu	Ser	Ser	Gly	Ser 425	Arg	Ser	Ser	Ser	Leu 430	Lys	Ser
Xaa	G1n	Gly 435	Thr	Gly	Phe	Glu	Leu 440	Gly	G1n	Leu	Gln	Ser 445	Ile	Arg	Ser
Glu	Gly. 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	Ala 460	Asn	Gln	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
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 Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp 35
 40
 45

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 Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Gln Arg Thr Leu

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		115	,				120					125				
		Phe					Val		aca Thr							432
	Glu					Ala			gtg Val		Asn				-	480
									cag Gln 170							528
			ctg Leu 180				tag *									552
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Glu	Lys	A1a 35	Glu	Ala	Ala	Ala	Thr 40	Leu	Lys	Ala	Ala	Pro 45	Gly	Trp	Leu	
	Arg 50	Phe	Leu	Val	Trp	Lys 55	Pro	Arg	Pro	Ala	Ser 60	Ala	Arg	Ala	Gln	
Pro 55	Gly	Leu	Val	Gln	G1u 70	Ala	Ala	Gln	Pro	G1n 75	Gly	Ser	Thr	Ser	Glu 80	
	Pro	Trp	Asn	Thr 85		Ile	Pro	Leu	Pro 90		Cys	Trp	Asp	G1n 95		
Phe	Leu	Thr	Asn 100		Thr	Phe	Leu	Lys 105	Val	Leu	Leu	Trp	Leu 110		Leu	
_eu	Gly	Leu 115	Phe	Val	Glu	Leu	G1u 120	Phe	Gly	Leu	Ala	Tyr 125		Val	Leu	
Ser	Leu 130		Tyr	Trp	Met	Tyr 135		Gly	Thr	Arg	Gly 140		Glu	Glu	Lys	
.ys		Glv	Glu	Lvs	Ser		Tvr	Ser	Val	Phe		Pro	Glv	Cvs	Glu	

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											gcc Ala 60				-	192
	_		_	-		-	-	-	-		ttt Phe	-	_			240
											aaa Lys					288
cag G1n							_		-				-	-	-	336

			aat Asn										384
			cag Gln								-		432
			aca Thr			_		-		-			480
		_	gtt Val 165	_	-	-	-		-	-		_	528
		_	cat His		_		-		-		_	-	576
	_	-	tgt Cys		-	-	-						624
			aga Arg										672
			ctt Leu		-					_	-	-	720
			gtg Val 245			-						cag· Gln	768
			gat Asp						-			-	816
			gaa Glu		Glu							ttc Phe	864

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250

Thr Arg Ser Arg Asp Arg Ser Leu Leu Pro Ser Asp Asp Glu Leu Lys

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Ser	Asn 290	Arg	Phe	Pro	Arg	Trp 295	Val	Pro	Trp	Met	Val 300	Lys	Ser	Glu		
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											aag Lys					144
											gct Ala 60					192
				_	_			_		-	cct Pro	_			_	240
											ttt Phe					288
											gtt Val					336

				_	-						cta Leu		384
	Ψ,	-			_	-					caa Gln	-	432
_		-		-		-	-		-	-	gaa Glu		480
											gac Asp 175		528
	_	•	-				-	_	-		cag G1n		576
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				ata Ile 245				tga *					750

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<221> misc_feature

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			ggc Gly		-	_	_		-			_	-	_	-	1	.92
			tcc Ser												-	2	240
		-	gca Ala			_		-		-			_	_		2	288
			tgg Trp 100			-										3	36
	-		gac Asp		-			_	-		_	-	-		-	3	84
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			gtg Val													4	80
_			tcc Ser				_	-		-					_	5	28

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	999 Gly															576
	gag Glu						_									624
	agc Ser 210	-			_		_	_	-					-		672
	aca Thr															720
	gac Asp											-		-		768
	cgg Arg															816
	gat Asp								tga *							846
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Val Thr Lys Pro Thr Ala Met Ala Gln Gly Arg Val Ala His Leu Ile
                            40
Glu Trp Lys Gly Trp Ser Lys Pro Ser Asp Ser Pro Ala Ala Leu Glu
                        55
Ser Ala Phe Ser Ser Tyr Ser Asp Leu Ser Glu Gly Glu Gln Glu Ala
Arg Phe Ala Ala Gly Val Ala Glu Gln Phe Ala Ile Ala Glu Ala Lys
                85
                                    90
Leu Arg Ala Trp Ser Ser Val Asp Gly Glu Asp Ser Thr Asp Asp Ser
                                105
Tyr Asp Glu Asp Phe Ala Gly Gly Met Asp Thr Asp Met Ala Gly Gln
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Leu Pro Leu Gly Pro His Leu Gln Asp Leu Phe Thr Gly His Arg Phe
                                            140
                        135
Ser Arg Pro Val Arg Gln Gly Ser Val Glu Pro Glu Ser Asp Cys Ser
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Gln Thr Val Ser Pro Asp Thr Leu Cys Ser Ser Leu Cys Ser Leu Glu
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Asp Gly Leu Leu Gly Ser Pro Ala Arg Leu Ala Ser Gln Leu Leu Gly
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Asp Glu Leu Leu Leu Ala Lys Leu Pro Pro Ser Arg Glu Ser Ala Phe
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Arg Ser Leu Gly Pro Leu Glu Ala Gln Asp Ser Leu Tyr Asn Ser Pro
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Leu Thr Glu Ser Cys Leu Ser Pro Ala Glu Glu Glu Pro Ala Pro Cys
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Lys Asp Cys Gln Pro Leu Cys Pro Pro Leu Thr Gly Ser Trp Glu Arg
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			_					-	_				•	atc Ile			240
		-			-			_						gcc Ala 95			288
			-		-		-				_	_		ttc Phe			336
														tac Tyr			384
														ctg Leu			432
					-									cgg Arg			480
-			Āla					-			-			gcc Ala 175			528

										gtg Val					576
					_					ccc Pro					624
					-		-			ctt Leu				-	672
		_		_	_					acc Thr 235	-	-		_	720
										ctg Leu					768
										gtc Val					816
								_		att					864
-	_	_	_	_					-	tac Tyr	_		_		912
-					G1n	Pro	-	His		ctg Leu 315			-		960
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-				-	-				_	ttt Phe				 _	1056

	tgt Cys															1104
	cct Pro 370				-	-								-		1152
_	cac His		-	-	_					-			-	_	-	1200
	aaa Lys												-		_	1248
	atg Met	-		_	_								-			1296
	gct Ala															1344
-, -	ctg Leu 450	taa *			•											1353
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M-+		<001		۸7 -	т	1		Dia -	W-7	<b>01</b>	1	1	۸٦.	Ć	0	
Met 1	Leu	VdI	1111.	5 5	ıyı.	Leu	Ald	Pne	10	uly	Leu	Leu	Ald	5er 15	cys	
Leu	Gly	Leu	G1u 20	Leu	Ser	Arg	Cys	Arg 25	Ala	Lys	Pro	Pro	G1y 30	Arg	Ala	
Cys	Ser	Asn 35		Ser	Phe	Leu	Arg 40		Gln	Leu	Asp	Phe 45		Gln	Val	
Tyr	Phe 50		Ala	Leu	Ala	A1a 55		Trp	Leu	G1n	Ala 60		Tyr	Leu	Tyr	

Lys 65	Leu	Tyr	Gln	His	Tyr 70	Tyr	Phe	Leu	Glu	G1y 75	Gln	Ile	Ala	Пe	Leu 80
Tyr	Val	Cys	G1y	Leu 85	Ala	Ser	Thr	Val	Leu 90	Phe	Gly	Leu	Val	.A] a 95	Ser
Ser	Leu	Val	Asp 100	Trp	Leu	Gly	Arg	Lys 105	Asn	Ser	Cys	Val	Leu 110	Phe	Ser
Leu	Thr	Tyr 115	Ser	Leu	Cys	Cys	Leu 120	Thr	Lys	Leu	Ser	G1n 125	Asp	Tyr	Phe
Val	Leu 130	Leu	Val	G1y	Arg	Ala 135	Leu	Gly	Gly	Leu	Ser 140	Thr	Ala	Leu	Leu
Phe 145	Ser	Ala	Phe	Glu	Ala 150	Trp	Tyr	Ile	His	G1u 155	His	Val	Glu	Arg	His 160
Asp	Phe	Pro	Ala	G1u 165	Trp	Ile	Pro	Ala	Thr 170	Phe	Ala	Arg	Ala	Ala 175	Phe
Trp	Asn	His	Val 180	Leu	Ala	Val	Val	Ala 185	Gly	۷a٦	Ala	Ala	G1u 190	Ala	Val
Ala	Ser	Trp 195	Ile	Gly	Leu	Gly	Pro 200	Val	Ala	Pro	Phe	Va1 205	Ala	Ala	Πe
Pro	Leu 210	Leu	Ala	Leu	Ala	Gly 215	Ala	Leu	Ala	Leu	Arg 220	Asn	Trp	Gly	Glu
Asn 225	Tyr	Asp	Arg	Gln	Arg 230	Ala	Phe	Ser	Arg	Thr 235	_	Ala	Gly	Gly	Leu 240
Arg	Cys	Leu	Leu	Ser 245	Asp	Arg	Arg	Val	Leu 250	Leu	Leu	Gly	Thr	Ile 255	Gln
Ala	Leu	Phe	G1u 260	Ser	Val	Ile	Phe	Ile 265	Phe	Val	Phe	Leu	Trp 270	Thr	Pro
Val	Leu	Asp 275	Pro	His	Gly	Ala	Pro 280	Leu	Gly	Ile	Пe	Phe 285	Ser	Ser	Phe
Met	Ala 290	Ala	Ser	Leu	Leu	Gly 295	Ser	Ser	Leu	Tyr	Arg 300	Ile	Ala	Thr	Ser
Lys 305	Arg	Tyr	His	Leu	Gln 310	Pro	Met	His	Leu	Leu 315	Ser	Leu	Ala	Val	Leu 320
Ile	Val	Val	Phe	Ser 325	Leu	Phe	Met	Leu	Thr 330	Phe	Ser	Thr	Ser	Pro 335	Gly
G1n	Glu	Ser	Pro .340	Val	Glu	Ser	Phe	Ile 345	Ala	Phe	Leu	Leu	11e 350	Glu	Leu
Ala	Cys	Gly 355	Leu	Tyr	Phe	Pro	Ser 360	Met	Ser	Phe	Leu	Arg 365	Arg	Lys	Val
Пe	Pro 370	Glu	Thr	Glu	Gln	A1a 375	Gly	Val	Leu	Asn	Trp 380	Phe	Arg	Val	Pro
Leu 385	His	Ser	Leu	Ala	Cys 390	Leu	Gly	Leu	Leu	Va1 395	Leu	His	Asp	Ser	Asp 400
Arg	Lys	Thr	Gly	Thr 405	Arg	Asn	Met		Ser 410	He	Cys	Ser	Ala	Val 415	Met

Val	Met	Ala	Leu 420	Leu	Ala	Val	Val	Gly 425	Leu	Phe	Thr	Val	Va1 430	Arg	His	
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_			ctc Leu		_	_				_		-	-	_	-	240
-			gga Gly	-				_	-							288

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						tcc Ser				tga *						465
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1	Ala	Gly	Pro	·5	-	Asp Cys			10					15		
1 Leu	Ala Tyr	Gly Gln	Pro Ala 20	·5 Ala	His	·	Val	Leu 25	10 Ala	Gln	Asp	Pro	G1u 30	15 Asn	Gln	
1 Leu Ala	Ala Tyr Leu	Gly Gln Ala 35	Pro Ala 20 Arg	·5 Ala Phe	His Tyr	Cys	Val Tyr 40	Leu 25 Thr	10 Ala Glu	Gln Arg	Asp Thr	Pro Ile 45	Glu 30 Ala	15 Asn Lys	Gln Xaa	
1 Leu Ala Leu	Ala Tyr Leu Val 50	Gly Gln Ala 35 Leu	Pro Ala 20 Arg Arg	·5 Ala Phe Arg	His Tyr Asp	Cys Cys Pro	Val Tyr 40 Ser	Leu 25 Thr	10 Ala Glu Lys	Gln Arg Arg	Asp Thr Thr 60	Pro Ile 45 Leu	Glu 30 Ala Cys	15 Asn Lys Arg	Gln Xaa Gly	
l Leu Ala Leu Cys 65	Ala Tyr Leu Val 50 Ser	Gly Gln Ala 35 Leu Ser	Pro Ala 20 Arg Arg Leu	·5 Ala Phe Arg Leu	His Tyr Asp Val 70	Cys Cys Pro 55	Val Tyr 40 Ser Gly	Leu 25 Thr Val	10 Ala Glu Lys Thr	Gln Arg Arg Cys 75	Asp Thr Thr 60 Thr	Pro Ile 45 Leu Gln	Glu 30 Ala Cys	15 Asn Lys Arg Gln	Gln Xaa Gly Arg 80	
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l Leu Ala Leu Cys 65 Arg	Ala Tyr Leu Val 50 Ser Cys	Gly Gln Ala 35 Leu Ser Arg Gln Glu	Pro Ala 20 Arg Arg Leu Gly Arg 100	Phe Arg Leu Gin 85 Phe	His Tyr Asp Val 70 Arg Leu	Cys Cys Pro 55 Pro	Val Tyr 40 Ser Gly Thr Asp	Leu 25 Thr Val Leu Val Pro 105	10 Ala Glu Lys Thr Gln 90 Gly	Gln Arg Arg Cys 75 Thr	Asp Thr Thr 60 Thr Cys Leu	Pro Ile 45 Leu Gln Leu Leu	Glu 30 Ala Cys Arg Thr	15 Asn Lys Arg Gln Cys 95 Gly	Gln Xaa Gly Arg 80 Gln Asp	
l Leu Ala Leu Cys 65 Arg Arg	Ala Tyr Leu Val 50 Ser Cys Ser Pro	Gly Gln Ala 35 Leu Ser Arg Gln Glu 115	Pro Ala 20 Arg Arg Leu Gly Arg 100 Ala	Phe Arg Leu Gin 85 Phe Gin	His Tyr Asp Val 70 Arg Leu	Cys Cys Pro 55 Pro Trp Asn	Val Tyr 40 Ser Gly Thr Asp Ser 120	Leu 25 Thr Val Leu Val Pro 105 Gln	10 Ala Glu Lys Thr Gln 90 Gly	Gln Arg Arg Cys 75 Thr His	Asp Thr Thr 60 Thr Cys Leu Ser	Pro Ile 45 Leu Gln Leu Leu Lys 125	Glu 30 Ala Cys Arg Thr Trp 110 Pro	15 Asn Lys Arg Gln Cys 95 Gly Leu	Gln Xaa Gly Arg 80 Gln Asp Gln	

WO 01/29221

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		acc Thr														240	
	-	gtg Val	-		-			-		-						288	
		gct Ala														336	
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cac	tga															390	

96

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<213> Homo sapiens

<400> 150

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Ala Ala Ala Val Ala Val Leu Val Ala Ser Val Tyr Pro Arg Lys Pro 35 40 45

Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn 50 55 60

Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg 65 70 75 80

Gly Val Val Cys Arg Leu Ser Arg Ser Leu Gln Glu His His Gly Leu 85 90 95

Pro Pro Ala Gly Leu Cys Arg Gln Pro Ala Lys Ala Arg Pro Gln Asp 100 105 110

Ala Pro Gly Thr Leu Arg Leu Arg Val Leu Gly Arg Gln Pro Gln Gly 115 120 125

His

<210> 151

<211> 567

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(567)

<400> 151

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1 5 10 15

gcc ctg ctg gga gtc ttc tgc gtg gcc atc ttc atc ttc ttg gtc aat

Ala	Leu	Leu	Gly 20	Val	Phe _.	Cys	Val	Ala 25	Ile	Phe	Ile	Phe	Leu 30	Val	Asn	
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-								ccc Pro						_		192
							-	cag Gln								240
						-		ccc Pro								288
	-			-	-			cct Pro 105						-		336
			-	-				gct Ala								384
								cct Pro								432
	-		~		-	~ ~	-	tcc Ser				-			~ ~	480
								atg Met								528
				_				cgg Arg 185		-		tga *				567

217

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Gly Val Val Phe Val Leu Arg Tyr Gln Arg Lys Glu Pro Pro Asp Ser
Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
                                    90
Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
                                105
Ser Ser Thr Leu Ala Arg Lys Glu Ala Gly Gly Arg Arg Lys Arg Val
Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
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                                            140
Pro Val Gly Ala Pro Ala Val Gln Ser Ile Leu Val Ala Gly Glu Glu
                    150
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Asp Ile Arg Trp Val Cys Glu Asp Met Gly Leu Lys Asp Pro Glu Glu
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                                    170
Leu Arg Asn Tyr Met Glu Arg Ile Arg Gly Ser Ser
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Met Ala Thr Gly Thr Arg Tyr Ala Gly Lys Val Val Val Thr Gly
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PCT/US00/29052

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				-		-				gag Glu			-		_	144
		-						-		atc Ile						192
-	-	-	-		_		_	-		gag Glu 75			-	-		240
										ggc Gly						288
-							-	-		ttc Phe		_	-	•		336·
_			_		-			_		aag Lys		_				384
										atc Ile						432
_	Пе	Gly	-	Ala	Gln	Ala	Val	Pro	Tyr	gtg Val 155	Ala	Thr	Lys		-	480
_		-	-			-	_	Ā٦a	-	gat Asp	-	-				528
										atc Ile						576

				-		Asp		 gcc Ala			_		624
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-	aac Asn	 _	tga *										735

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<212> PRT

<213> Homo sapiens

<400> 154

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Val	Thr	Ala	Met	Thr 165	-	Ala	Leu	Ala	Leu 170	,	Glu	Ser	Pro	Tyr 175	•	
Val	Arg	Val	Asn 180	Cys		Ser	Pro	Gly 185			Trp	Thr	Pro 190	_	Trp	
G1u	Glu	Leu 195	Ala	Ala	Leu	Met	Pro 200	Asp	Pro	Arg	Ala	Thr 205	Ile	Arg	Glu	
Gly	Met 210		Pro	Ser	His	Trp 215	Ala	Ala	Trp	Ala	Ser 220	Pro	Leu	Arg	Ser	
225			Gln	Cys	Ser 230	Trp	Pro	Pro	Lys	Pro 235	Thr	Ser	Ala	Arg	Ala 240	
Leu	Asn	Cys	Ser													
			155 975													
			DNA													
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		220>														
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			miso			<b>.</b>										
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	<'	223>	n =	A,T	.C or	^ G										
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1				5					10					15	•	
			gag									_				96
1111	пр	Ald	Glu 20	ыу	met	uly	Leu	25	Pro	Pro	GIU	Leu	30	ыу	ser	
gcc	tct	CCC	agc	cgg	tac	cat	999	cct	gcc	cgc	tgg	atg	ССС	cca	cgc	144
Ala	Ser	Pro 35	Ser	Arg	Tyr	His	Gly 40	Pro	Ala	Arg	Trp	Met 45	Pro	Pro	Arg	
taa	acc	റമന	ggt	acc	cct	กลต	cta	nan	cad	aaa	cac		Cac	caa	C20	192
	Ala		Gly													1.7.
	50					55					60					
att	gtg	tcc	tgg	ttc	gcc	gac	cac	ссс	cgg	gcc	CCC	ttt	ggc	cta	cac	240

11e 65	Val	Ser	Trp	Phe	A1a 70	Asp	His	Pro	Arg	Ala 75	Pro	Phe	Gly	Leu	His 80	
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			-		_	_							gtg Val 110		-	336
													gac Asp			384
-		-	_			-							gac Asp			432
													ctg Leu			480
					-		-						ctc Leu	-		528
_		-	-	_			_						cac His 190			576
													gac Asp			624
													ccc Pro			672
													aag Lys			720
сса	agc	tgt	acc	gtg	ggc	ttc	tat	gct	gga	gac	agg	aag	gag	ttt	gag	768

Pro	Ser	Cys	Thr	Va1 245	Gly	Phe	Tyr	Ala	Gly 250	Asp	Arg	Lys	Glu	Phe 255	Glu	
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				atg Met									_	_		864
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<400> 156

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Ala Ser Pro Ser Arg Tyr His Gly Pro Ala Arg Trp Met Pro Pro Arg 35 40 45

Trp Ala Gln Gly Ala Pro Glu Leu Glu Gln Glu Arg Arg His Arg Gln 50 55 60

Ile Val Ser Trp Phe Ala Asp His Pro Arg Ala Pro Phe Gly Leu His

65					70					/5					80
Ar	g Leu	Val	Glu	Leu 85	Gly	Gln	Ser	Ser	Gly 90	Lys	Lys	Ala	Gly	Asp 95	Trp
Ту	r Gly	Pro	Ser 100	Leu	Val	Ala	His	Ile 105	Leu	Arg	Lys	Ala	Val 110	Glu	Ser
Cy:	s Ser	Asp 115	Val	Thr	Arg	Leu	Val 120	Val	Tyr	Val	Ser	G1n 125	Asp	Cys	Thr
۷a	1 Tyr 130	Lys	Ala	Asp	Val	Ala 135	Arg	Leu	Val	Ala	Arg 140	Pro	Asp	Pro	Thr
A1:	a Glu 5	Trp	Lys	Ser	Va7 150	Val	He	Leu	Val	Pro 155	Val	Arg	Leu	Gly	Gly 160
	u Thr			165		•			170					175	
Cy:	s Glu	Leu	Cys 180	Leu	Gly	Ile	Met	Gly 185	Gly	Lys	Pro	Arg	His 190	Ser	Leu
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Туі	r Cys 210	GIn	Pro	Thr	Val	Asp 215	Val	Ser	Gln	Ala	Asp 220	Phe	Pro	Leu	Glu
Sei 22!	r Phe 5	His	Cys	Thr	Ser 230	Pro	Arg	Lys	Met	Ala 235	Phe	Ala	Lys	Met	Asp 240
Pro	o Ser	Cys	Thr	Va1 245	Gly	Phe	Tyr	Ala	Gly 250	Asp	Arg	Lys	Glu	Phe 255	Glu
Thi	r Leu	Cys	Ser 260	Glu	Leu	Thr	Arg	Val 265	Leu	Ser	Ser	Ser	Ser 270	Ala	Thr
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Sei	²⁹⁰	Asp	Asp	Leu	Cys	Ser 295	Gln	Leu	Ala	Gln	Pro 300	Thr	Leu	Arg	Leu
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Tyr				ttc Phe							480
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				gca Ala							576
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	Glu			cta Leu	Gln						768

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Ala	Gln	Ala	Gln	Leu 325			Ala	Lys	G1u 330	Arg		Gln	Gln	G1 <i>y</i> 335		
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G1n 385	Glu	Thr	Val	Glu	Met 390	Asp	Ile	Arg	Пе	G1y 395		Val	Glu	His	Thr 400	
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	tac Tyr															144
	agc Ser 50															192

	G1n										Glu				gac Asp 80	240
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		Gly	cag Gln				۷a٦					Ala				432
	Trp		tgt Cys								Leu					480
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Val																

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Pro	Ser	Val	Glu 180	Asn	Val	Arg	Thr	Ser 185	Leu	Glu	Gly	Tyr	Pro 190	Ala	Gly	
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	290					295					G1u 300					
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	aag Lys										288
	gtt Val 100										336
	cgc Arg										384
	atg Met										432
	aaa Lys										480
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Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala
Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
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                                    90
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
                                105
Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
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Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
                    150
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Pro Pro Ser Gly Pro Ala Pro Gln Tyr Pro Leu Tyr Pro Ala Gly Pro
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														gca Ala		240
														ctc Leu 95		288
														att Ile		336
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			Gly											gga Gly 175		528

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gag Glu	ctt Leu	gaa Glu 195	ı Ser	cct Pro	aaa Lys	tgt Cys	aaa Lys 200	Arg	cag Gln	gaa Glu	aat Asn	gag Glu 205	Gln	cta Leu	ctg Leu	624
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Arg	Gly	Ala 35		Thr	Pro	Glu	Tyr 40		Val	Ala	Asn	Val 45		Ser	Val	
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Asp	Cys	His 115		Gly	Leu	Leu		Pro	Leu		Pro	Leu 125		Glu	Gly	
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AIU	LCU	JCI	uiy	165	Uy S	Uy S	val	ΑΙα	170	Leu	1111	Leu	Arg	175	Vdl	
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									gtc Val 90							288
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Leu Gln Tyr Leu Phe Glu Asn Ile Ser Gln Leu Thr Glu Lys Asp Val 35 40 45

Ser Thr Thr Val Ser Arg Lys Ala Trp Gly Ala Glu Ala Val Gly Cys 50 55 60

Ser Ile Gln Leu Thr Thr Pro Val Asn Val Leu Val Ile His His Val 65 70 75 80

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20 25 30

			Asp					Ala				cac His 45	Pro		aac Asn		144
		Leu										gtg Val					192
											Leu	agg Arg					240
												aag Lys					288
												atg Met					336
												cgg Arg 125				-	384
												ctg Leu		_		•	432
												acc Thr				4	480
												cag Gln				ţ	528
												ctc Leu				į	576
tct Ser	His	tca Ser 195	gta Val	ctc Leu	tat Tyr	Met	cgg Arg 200	ggc Gly	cgg Arg	ctg Leu	gct Ala	gag Glu 205	gtg Val	aag Lys	ggc Gly	. (	524

	ctg Leu 210															67.	2
	gat Asp															72	0
	ggc Gly										_	_	_			76	8
	cag G1n															810	5
	gcc Ala									-	-				_	864	4
	gag Glu 290															912	2
	gag Glu		tga *													924	1
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1et 1	<4 Glu	00> G1n		Gln 5	Glu	Ala	Leu	Lys	Val 10	Arg	Lys	Asp	Asp	Ala 15	His		
∖la	Leu		Leu 20	Leu	Ala	Leu		Phe 25	Ser	Ala	G1n	Lys	His 30		Gln		
lis	Ala			Val	Val				Ile	Thr	Glu	His 45		Glu	Asn		
	Asn 50		Met	Phe				Lys	Leu		Gln 60	-	Leu	Lys	Gly		

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Pro Glu Glu Ala Leu Val Thr Cys Arg Gln Val Leu Arg Leu Trp Gln
                    70
                                        75
Thr Leu Tyr Ser Phe Ser Gln Leu Gly Gly Leu Glu Lys Asp Gly Ser
Phe Gly Glu Gly Leu Thr Met Lys Lys Gln Ser Gly Met His Leu Thr
            100
                                105
Leu Pro Asp Ala His Asp Ala Asp Ser Gly Ser Arg Arg Ala Ser Ser
                            120
Ile Ala Ala Ser Arg Leu Glu Glu Ala Met Ser Glu Leu Thr Met Pro
                        135
Ser Ser Val Leu Lys Gln Gly Pro Met Gln Leu Trp Thr Thr Leu Glu
                    150
                                        155
Gln Ile Trp Leu Gln Ala Ala Glu Leu Phe Met Glu Gln Gln His Leu
                165
                                    170
Lys Glu Ala Gly Phe Cys Ile Gln Glu Ala Ala Gly Leu Phe Pro Thr
                                185
Ser His Ser Val Leu Tyr Met Arg Gly Arg Leu Ala Glu Val Lys Gly
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Asn Leu Glu Glu Ala Lys Gln Leu Tyr Lys Glu Ala Leu Thr Val Asn
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                                            220
Pro Asp Gly Val Arg Ile Met His Ser Leu Gly Leu Met Leu Ser Arg
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Leu Gly His Lys Ser Leu Ala Gln Lys Val Leu Arg Asp Ala Val Glu
                                    250
Arg Gln Ser Thr Cys His Glu Ala Trp Gln Gly Leu Gly Glu Val Leu
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Gln Ala Gln Gly Gln Asn Glu Ala Ala Val Asp Cys Phe Leu Thr Ala
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	-		-					tct Ser							~	144
								cat His								192
				_		_		cca Pro				-	_		4	240
	-			-	_			atg Met					~			288
					_	-		aca Thr 105								336
							_	gtt Val						_		384
								cac His								432
_			-					act Thr	-			-	-	•		480
gga	tca	aaa	ttt	gat	act	<b>9</b> 99	agc	ttt	gtt	ggt	ggt	att	gta	tta	acg	528

Gly	' Ser	Lys	Phe	Asp 165	Thr	Gly	Ser	Phe	Val 170	Gly	Gly	Ile	Val	Leu 175		
			tta Leu 180													576
			att Ile										Ala			624
taa *																627
	<	211> 212>	176 208 PRT Homo	o sap	oiens	5										
	<		VARI													
			(1). Xaa			nino	Acid	d								
Met	</td <td>223&gt; 400&gt;</td> <td>Xaa</td> <td>= Ar</td> <td>у Ап</td> <td></td> <td></td> <td></td> <td>А]а 10</td> <td>Ala</td> <td>Leu</td> <td>Leu</td> <td>Leu</td> <td>Gl<i>y</i> 15</td> <td>Thr</td> <td></td>	223> 400>	Xaa	= Ar	у Ап				А]а 10	Ala	Leu	Leu	Leu	Gl <i>y</i> 15	Thr	
1	<pre>Gly</pre>	223> 400> Leu	Xaa 176	= Ar Ala 5	iy An Arg	Gly	Ala	Trp	10				Ala	15		
1 Leu	<pre>Gly Gln</pre>	223> 400> Leu Val Ser	Xaa 176 Gly Leu	= Ar Ala 5 Ala	ny An Arg Leu	Gly Leu	Ala Gly	Trp Ala 25	10 Ala	His	Glu	Ser His	Ala 30	15 Xaa	Met	
1 Leu Ala	Gly Gln Ala	223> 400> Leu Val Ser 35	Xaa 176 Gly Leu 20	= Ar Ala 5 Ala Asn	ny An Arg Leu Ile	Gly Leu Glu Leu	Ala Gly Asn 40	Trp Ala 25 Ser	10 Ala Gly	His Leu Pro	Glu Pro Ser	Ser His 45	Ala 30 Asn	15 Xaa Ser	Met Ser	
1 Leu Ala Ala	Gly Gln Ala Asn 50	223> 400> Leu Val Ser 35 Ser	Xaa 176 Gly Leu 20 Ala	= Ar Ala 5 Ala Asn Glu	Arg Leu Ile Thr	Gly Leu Glu Leu 55	Ala Gly Asn 40 Gln	Trp Ala 25 Ser His	10 Ala Gly Val	His Leu Pro	Glu Pro Ser 60	Ser His 45 Asp	Ala 30 Asn His	15 Xaa Ser Thr	Met Ser Asn	
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	130					135					140					
Ala 145	Ser	Ser	Val	Thr	Ile 150		Thr	Thr	Met	His 155	Ser	Glu	Ala	Lys	Lys 160	
Gly	Ser	Lys	Phe	Asp 165	Thr	Gly	Ser	Phe	Val 170	Gly	Gly	Ile	Val	Leu 175	Thr	
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n+~		100>		+++	o+ o	~~~	~~+	~~~	+~~	a+a	<b></b>	n=+	~~+	~++		40
				tct Ser 5												48
				gtt Val						-					-	96
				gct Ala												144
				aaa Lys												192
				gat Asp											_	240

				-	acc Thr	_		-		_	-	-	•	288
					cgg Arg									336
					gac Asp									384
					cat His 135	-		_	_					432
					gtc Val									480
-				-	tta Leu	_		_				-	-	528
		_			tgg Trp						_			576
_		-			ggt Gly		-	_	_		-	-		624
			-		ggc Gly 215	-	_							672
					ctg Leu									 _. 720
					gag Glu							-	_	768

			tct Ser 260													81	.6
			acg Thr													86	54
			cag Gln													91	2
			tac Tyr		_				_			-	_		-	96	0
			gct Ala													100	8
			gcg Ala 340													105	6
			agg Arg													110	4
			cag Gln													115	2
			gtg Val													120	0
			atc Ile													124	3
aag Lys	atc Ile	ttg Leu	ctg Leu 420	cac His	ggt Gly	ttg Leu	Trp	tac Tyr 425	gaa Glu	ctg Leu	ttt Phe	gga Gly	gga Gly 430	aac Asn	ccc Pro	129	5

ASN ASN LE	g ccc a u Pro S 5	gc aca er Thr	agg Arg	ggt Gly 440	Leu	cag Gln	tgt Cys	gga Gly	cgt Arg 445	Gly	ctg Leu	acc Thr	1344
agg gcc ac Arg Ala Th 450									Thr				1392
tta aac tg Leu Asn * 465	a ·												1401
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Met Val Try 1 Cys Asp Arg Trp Ile Ile	Ala Se I I Thr Va 20 Ile A	o al Val a Ala	Asn Thr	Gly Val 40	Ile 25 Val	10 Ile Ser	Ala Ile	Thr Ile	Val Ile 45	Val 30 Val	15 Val Phe	Ser Asp	
Met Val Try 1 Cys Asp Arg Trp Ile Ile 35 Pro Leu Gly 50 Leu Asp Ser	O Ala Se I Thr Va 20 E Ile A Gly Ly	ol Val a Ala s Met	Asn Thr Ala 55	Gly Val 40 Pro	Ile 25 Val Tyr	10 Ile Ser Ser	Ala Ile Ser Asn	Thr Ile Ala 60	Val Ile 45 Gly	Val 30 Val Pro	15 Val Phe Ser	Ser Asp His	
Met Val Tri 1 Cys Asp Arg Trp Ile Ile 35 Pro Leu Gly 50 Leu Asp Ser 65	Ala Se Thr Va 20 E Ile A Gly Ly	al Val a Ala s Met p Ser 70	Asn Thr Ala 55 Ser	Gly Val 40 Pro Gln	Ile 25 Val Tyr Leu	10 Ile Ser Ser Leu	Ala Ile Ser Asn 75	Thr Ile Ala 60 Gly	Val Ile 45 Gly Leu	Val 30 Val Pro	15 Val Phe Ser Thr	Ser Asp His Ala 80	
Met Val Try 1 Cys Asp Arg Trp Ile Ile 35 Pro Leu Gly 50 Leu Asp Ser	Ala Se Thr Va 20 E Ile A Gly Ly	Silval a Ala s Met sp Ser 70 sp Glu	Asn Thr Ala 55 Ser	Gly Val 40 Pro Gln	Ile 25 Val Tyr Leu	10 Ile Ser Ser Leu	Ala Ile Ser Asn 75	Thr Ile Ala 60 Gly	Val Ile 45 Gly Leu	Val 30 Val Pro	15 Val Phe Ser Thr	Ser Asp His Ala 80	
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Ala	Asp	Leu	Asp	Ala 165		Leu	Glu	ı Asn	Cys 170		His	Tyr	· Met	Gln 175	
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Thr	Gly	Leu 195		Arg	Ile	Gly	Gly 200		Cys	Cys	Arg	Ser 205	Arg	Thr	Thr
	210					215					220		Phe	_	
225					230					235			His		240
Phe	His	Asp	Lys	Val 245		Glu	Leu	Pro	Phe 250		Val	Ala	Leu	Asp 255	
			260					265					Ser 270		
		275					280					285			
	290					295					300		Gln		
305					310					315			Ser		320
				325					330				His	335	
Gly	Xaa	Gly	A1a 340	Ala	Ala	Leu	Leu	Ala 345	Thr	Met	Leu	Arg	A1a 350	Ala	Tyr
Pro	Gln	Val 355	Arg	Cys	Tyr	Ala	Phe 360	Ser	Pro	Pro	Arg	G1y 365	Leu	Trp	Ser
Lys	Ala 370	Leu	Gln	Glu	Tyr	Ser 375	Gln	Ser	Phe	Ile	Val 380	Ser	Leu	Val	Leu
G1y 385	Lys	Asp	Val	Ile	Pro 390	Arg	Leu	Ser	Val	Thr 395	Asn	Leu	Glu	Asp	Leu 400
Lys	Arg	Arg	Пе	Leu 405	Arg	Val	Val	Ala	His 410	Cys	Asn	Lys	Pro	Lys 415	Tyr
Lys	Ile	Leu	Leu 420	His	Gly	Leu	Trp	Tyr 425	Glu	Leu	Phe	Gly	Gly 430	Asn	Pro
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Leu 465	Asn														

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			Cys										Ser	ttg Leu		144
														cta Leu		192
aat Asn 65	gac Asp	att Ile	ctt Leu	gtt Val	tca Ser 70	ggt Gly	gga Gly	aga Arg	atc Ile	aac Asn 75	agc Ser	cgt Arg	gat Asp	gtc Val	tgg Trp 80	240
														ctc Leu 95		288
aaa _ys	ggc Gly	aga Arg	tgg Trp 100	cgt Arg	cac His	aaa Lys	atg Met	gct Ala 105	gtc Val	ctc Leu	ctt Leu	ggt Gly	aaa Lys 110	gta Val	tat Tyr	336
														gaa Glu		384
at	gat	tcc	ttt	tca	aat	cga	tgg	act	gaa	gtt	gct	CCC	ctt	aag	gaa	432

Tyr	Asp 130	Ser	Phe	Ser	Asn	Arg 135	Trp	Thr	Glu	Val	Ala 140	Pro	Leu	Lys	Glu	
					-				_	-	ggc Gly		_		• •	480
					-	-			-		gat Asp	_	_			528
											gca Ala	_				576
			Cys			-	-				aac Asn				_	624
_			-		-	_			_		gat Asp 220		_	-	~	672
											cag Gln			-		720
											ggc Gly				-	768
			_		-				_		gat Asp		-		-	816
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Lys Leu Pro Glu Phe Thr Lys Ser Glu Tyr Ala Val Cys Ala Leu Arg
                        55
Asn Asp Ile Leu Val Ser Gly Gly Arg Ile Asn Ser Arg Asp Val Trp
                    70
Ile Tyr Asn Ser Gln Leu Asn Ile Trp Xaa Arg Val Ala Ser Leu Asn
Lys Gly Arg Trp Arg His Lys Met Ala Val Leu Leu Gly Lys Val Tyr
                                105
Val Val Gly Gly Tyr Asp Gly Gln Asn Arg Leu Ser Ser Val Glu Cys
                            120
                                                 125
Tyr Asp Ser Phe Ser Asn Arg Trp Thr Glu Val Ala Pro Leu Lys Glu
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Ala Val Ser Ser Pro Ala Val Thr Ser Cys Val Gly Lys Leu Phe Val
                    150
                                        155
Ile Gly Gly Pro Asp Asp Asn Thr Cys Ser Asp Lys Val Gln Ser
Tyr Asp Pro Glu Thr Asn Ser Trp Leu Leu Arg Ala Ala Ile Pro Ile
                                185
Ala Lys Arg Cys Ile Thr Ala Val Ser Leu Asn Asn Leu Ile Tyr Val
                            200
                                                205
Ala Gly Gly Leu Thr Lys Ala Ile Tyr Cys Tyr Asp Pro Val Glu Asp
                        215
                                            220
Tyr Trp Met His Val Gln Asn Thr Phe Ser Arg Gln Glu Asn Cys Gly
                    230
Met Ser Val Cys Asn Gly Lys Ile Tyr Ile Leu Gly Gly Arg Arg Glu
                                    250
Asn Gly Glu Ala Thr Asp Thr Ile Leu Cys Tyr Asp Pro Ala Thr Ser
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			260					265					270		
Пe	Ile	Thr 275	Gly		Ala	Ala	Met 280	Pro		Pro	Val	Ser 285	Tyr	Gly	
Cys	Va1 290	Thr		His	Arg	Tyr 295	Asn		Lys	Cys	Phe 300	Lys			
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						gtg Val									96
						anc Xaa									144
						gag Glu 55									192
						cca Pro									240
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									tca Ser							336
									acg Thr				_		_	384
	gta Val 130				-	tag *										405
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	Leu	His	Thr 20		Ala	۷a٦	Val	Leu 25	Leu	Val	Pro	Ser	Asp 30	-	Gly	
Arg	Ala	Phe 35	Leu	Leu	Arg	Xaa	Gly 40	Phe	Phe	Ile	Arg	Arg 45	Arg	Met	Tyr	
Pro	Pro 50	Pro	Leu	Ile	Glu	Glu 55	Pro	Ala	Phe	Asn	Val 60	Ser	Tyr	Thr	Arg	
G1n 65	Pro	Pro	Asn	Pro	G1y 70	Pro	Gly	Ala	Gln	G1n 75	Pro	Gly	Pro	Pro	Tyr 80	
Tyr	Thr	Asp		-	-	Pro	-		Asn 90	Pro	Val	Gly	Asn	Ser 95	Met	
				85												
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								 	-	acc Thr			96
										aga Arg			144
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										aaa Lys		;	240
-		-	-	-						gtg Val 95	•		288
										tct Ser		;	336
										tcc Ser		(	384

			agc Ser								_		_	432
			ctg Leu 150	_				_			_	_	•	480
			gaa Glu	-				_	-	-		- ,		528
			tat Tyr										-	576
			cag G1n	_	_	_	_		_			_		624
			cac His							-		-	-	672
			agg Arg 230									_		720
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			cac His					_						864
			gga Gly						tga *					900

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Pro Ser His Val Gln Leu Lys Val Val Ala Gly Asn His Asp Ile Gly
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Phe His Tyr Glu Met Asn Thr Tyr Lys Val Glu Arg Phe Glu Lys Val
Phe Ser Ser Glu Arg Leu Phe Ser Trp Lys Gly Ile Asn Phe Val Met
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Val Asn Ser Val Ala Leu Asn Gly Asp Gly Cys Gly Ile Cys Ser Glu
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Thr Glu Ala Glu Leu Ile Glu Val Ser His Arg Leu Asn Cys Ser Arg
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Glu Ala Arg Gly Ser Ser Arg Cys Gly Pro Gly Pro Leu Leu Pro Thr
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Ser Ala Pro Val Leu Leu Gln His Tyr Pro Leu Tyr Arg Arg Ser Asp
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Ala Asn Cys Ser Gly Glu Asp Ala Ala Pro Ala Glu Glu Arg Asp Ile
                                    170
Pro Phe Lys Glu Asn Tyr Asp Val Leu Ser Arg Glu Ala Ser Gln Lys
            180
                                185
Leu Leu Trp Trp Leu Gln Pro Arg Leu Val Leu Ser Gly His Thr His
                            200
                                                205
Ser Ala Cys Glu Val His His Gly Gly Arg Val Pro Glu Leu Ser Val
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                                            220
Pro Ser Phe Ser Trp Arg Asn Arg Asn Asn Pro Ser Phe Ile Met Gly
Ser Ile Thr Pro Thr Asp Tyr Thr Leu Ser Lys Cys Tyr Leu Pro Arg
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Glu	Asp	Val				Ile	Tyr	Cys	250 Gly		Val	Gly	Phe	255 Leu	Val	
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	· <		CDS	(-	453)											
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						tat Tyr										96
						aaa Lys										144
						ctg Leu 55										192
ctt Leu 65	gga Gly	tta Leu	gat Asp	gag Glu	tcc Ser 70	aag Lys	ctg Leu	cca Pro	gaa Glu	aaa Lys 75	att Ile	ata Ile	atg Met	aac Asn	tac Tyr 80	240
						cga Arg										288
						ccc Pro									_	336

<211> 1491

263

100 105 110 cga ctt tgt tac ctg aaa gag cag gaa gat att gca tgg tct gct ctt 384 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 125 gtg aag ttg ttt gat ccc gtg aaa tct ccc aga tgt tat gct gtt att 432 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 140 135 gcc ctg aag aag cag cag tga 453 Ala Leu Lys Lys Gln Gln * 145 150 <210> 186 <211> 150 <212> PRT <213> Homo sapiens <400> 186 Met Ser Ala Cys Leu Ala Leu Glu Arg Val Ala Ala Gly Gln Gly Leu Pro Thr Glu Ser Leu Phe Tyr Arg Ala Val Leu Gln Asp Ile Ile Lys Asp Cys Tyr Gly Ile Thr Lys Cys Asp Arg His Val Gly Lys Ile Tyr 40 Ser Lys Cys Ser Ser Phe Leu Asp Tyr Val Arg Arg Ser Leu Lys Lys 55 Leu Gly Leu Asp Glu Ser Lys Leu Pro Glu Lys Ile Ile Met Asn Tyr 70 75 Tyr Glu Lys Tyr Lys Pro Arg Met Asn Glu Leu Glu Ala Phe Asn Met 90 Leu Lys Val Val Leu Ala Pro Cys Ile Glu Thr Leu Ile Leu Leu Asp 105 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 125 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 Ala Leu Lys Lys Gln Gln 145 150 <210> 187

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										gcg Ála		96
										ccc Pro		144
										gcg Ala		192
										gtc Val		240
										gca Ala 95		288
										tca Ser		336
										gca Ala		384
41a										gcc Ala		432

						Val			gca Ala 160	480
						gat Asp			ctt Leu	528
		-	-	-		 ctt Leu	-	-		576
						gat Asp				624
						cag Gln 220				672
						tcc Ser				720
						gag Glu				768
						gga Gly				816
Gln						tcc Ser				864
						agt Ser 300				912
		Ser			Val	ccc Pro				960

ggg Gly										_		_		1	800
 cct Pro									 _		_			1	056
gtc Val														1	104
agc Ser 370											_	_	_	1	152
cac His		_	-			_			 _		_	_	•	1	200
gtg Val														1	248
acc Thr														1.	296
act Thr					-				-					1	344
cca Pro 450				Trp		-								13	392
gta Val	_		Cys		-			Arg	-	-		-	_	14	440
att Ile		Ala					Tyr							14	488

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267

tag 1491

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<211> 496

<212> PRT

<213> Homo sapiens

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250

Leu Val Val Leu Ser Gly Leu His Met Met Glu Gly Gln Ser Lys Glu

			260					265					270			
Leu	Gln	Arg 275	_	Arg	Leu	Leu	G1u 280	Val	Val	Thr	Ser	Ile 285	Ser	Asp	Ile	
Pro	Thr 290	Gly	Ile	Pro	Val	His 295	Leu	Glu	Leu	Ala	Ser 300	Met	Thr	Asn	Arg	
G1u 305	Leu	Met	Ser	Ser	Ile 310	Val	His	Gln		Phe 315	Pro	Ala	Val	Thr	Ser 320	
Leu	Gly	Leu	Asn	G1u 325	Gln	Glu	Leu	Leu	Phe 330	Leu	Thr	Gln	Ser	A1a 335		
Gly	Pro	His	Ser 340			Ser	Ser	Trp 345		Gly	Val	Pro	Asp 350		Gly	
Met	Val	Ser 355	Asp	Пe	Leu	Phe	Trp 360	He	Leu	Lys	Glu	His 365	Gly	Arg	Ser	
Lys	Ser 370	Arg	Ala	Ser	Asp	Leu 375	Thr	Arg	He	His	Phe 380	His	Thr	Leu	Va1	
Tyr 385	His	Пe	Leu	Ala	Thr 390	Val	Asp	Gly	His	Trp 395	Ala	Asn	Gln	Leu	Ala 400	
Ala	Val	Ala	Ala	Gly 405	Ala	Arg	Val	Ala	Gly 410	Thr	Gln	Ala	Cys	Ala 415	Thr	
Glu	Thr	Ile	Asp 420	Thr	Ser	Arg	Val	Ser 425	Leu	Arg	Ala	Pro	G1n 430	Glu	Phe	
Met	Thr	Ser 435	His	Ser	Glu	Ala	Gly 440	Ser	Arg	Ile	Val	Leu 445	Asn	Pro	Asn	
	450				•	455					460	Phe				
465					470	·				475		Gly		_	480	
Ala	Ile	Ser	Ala	G1u 485	Gly	Leu	Phe	Tyr	Ser 490	Glu	Val	His	Pro	His 495	Tyr	
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^+~		×00>		++-	<b>.</b>			<b>L.L.</b> 1		1	<b>.</b>		1			40
									-			atc Ile				48
1				5					10					15		

	ggt Gly		-			-		-		-			96	
	gcg Ala										-		144	
	tgt Cys 50												192	
	tac Tyr										-	-	240	
	tgg Trp												288	
	atc Ile		-	-	-			-	_	_	-	_	336	
tga *													339	

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<211> 112

<212> PRT

<213> Homo sapiens

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45 40 45 Ang Val Leu San Clu Leu Clu Leu Mat Clu Ala

Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 50 55 60

Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser

65 Pro	Trn	Thr	T lo	Thn	70	Mot	Val	Tlo	°	75	Can	110	۸٦.	Th	80	
				Thr 85					90					95		
Gly	Ile	Val	Val 100	Met	Ala	Asp	Pro	Lys 105		Lys	Ala	Tyr	Arg 110	Val	Val	
	<	21 <b>1&gt;</b> 212>	191 630 DNA Hom	o sap	oi ens	S										
	<		CDS	(6	530)											
ata		400>		atg	ac a	CC 3	tet	too	cta	200	ato	200	++>	000	000	4.0
				Met 5												48
				tgc Cys												96
				tgg Trp												144
				gga Gly												192
				gtt Val												240
				aag Lys 85										-		288
				gcc Ala												336

		-	_	_					gaa Glu		_			_	384
		-		_	-		-	-	ctg Leu	-		_	~		432
									aag Lys 155						480
									tgg Trp						528
									aaa Lys			-			576
						Пe			gag Glu						624
ttg Leu	tga *														630

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<211> 209

<212> PRT

<213> Homo sapiens

<400> 192

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1 5 10 15

Leu Ala Ser Ala Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly
20 25 30

Ala Ala Ser Leu Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln Ser Thr
35 40 45

Ser Tyr Leu Pro Gly Tyr Val Pro Lys Thr Ser Leu Ser Ser Pro Pro
50 55 60

Trp Pro Glu Val Val Leu Pro Asp Pro Val Glu Glu Thr Arg His His

65					70					75					80	
Αl	a Glu	Val	Val	Lys 85	Lys	Val	Asn	Glu	Met 90	Пe	۷a٦	Thr	Gly	G1n 95		
G1	y Arg	Leu	Phe 100		Val	Val	His	Phe 105	Ala	Ser	Arg	G1n	Trp 110	Lys	Val	
	r Ser	115	•				120					125			_	
	y Glu 130					135					140			·		
14					150					155	•				160	
	ı Ala			165					170					175		
	) Phe		180	·				185					190			
Pro	o Gln	Thr 195	Val	Leu	Arg	Ile	Asn 200	Ser	Пe	GTu	Ile	Ala 205	Pro	Cys	Leu	
Lei	J															
	<th>210&gt; 211&gt; 212&gt; 213&gt; 220&gt; 221&gt; 222&gt;</th> <th>351 DNA Homo</th> <th>,</th> <th></th> <th>S</th> <th></th>	210> 211> 212> 213> 220> 221> 222>	351 DNA Homo	,		S										
		400>														
	999 Gly			-		-										48
	ggt Gly															96
	gcg Ala															144
	tgt Cys															192

	50					55					60					
											gga Gly					240
											agt Ser					288
											ccc Pro					336
	cgc Arg		gtt Val	tga *												351
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Mat		100> Sor		Lou	Son	Cln	Dro	Dho	Glu	Son	Tyr	ΠA	Thn	۸٦٠	Dno	
1	uly	261	Arg	5	Sei .	GIII	FIU	riie	10	261	Tyt	116	1131	15	Pro	
Pro	Gly	Thr	Ala 20	Ala	Ala	Pro	Ala	Lys 25	Pro	Ala	Pro	Pro	Ala 30	Thr	Pro	
Gly	Ala	Pro 35	Thr	Ser	Pro	Ala	G1u 40	His	Arg	Leu	Leu	Lys 45	Thr	Cys	Trp	
Ser	Cys 50		Val	Leu	Ser	Gly 55		Gly	Leu		Gly 60		Gly	Gly	Tyr	
		Trp	Val	Ala			Pro	Met	Lys	Met	Gly	Tyr	Pro	Pro		
65 Pro	Trp	Thr			70 G1n	Met	Val	Ile		75 Leu	Ser	Glu	Asn		80 Gly	
Пe	Ala	Thr	Trp	85 Gly	Ile	Val	Val		90 Ala	Asp	Pro	Lys	Gly	95 Lys	Ala	
Гуr	Arg	Val 115	100 Val					105					110			
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							gaa Glu				96
							gtg Val				144
							ggc Gly				192
							acc Thr				240
							gag Glu 90		 -		288
							gga Gly				336
						-	gat Asp				384
							gag Glu				432

	gca Ala					-							-				480
	aag Lys																528
	ctg Leu					_		_	_		-	_		•			576
	aac Asn		-	-	_			-	_				_		-		624
	ttt Phe 210			-	_	-						_			_		672
	cca Pro	-				_	_	_	_	_		_		-	-		720
	tct Ser						-		-								768
	gga Gly				-	-									ctg Leu	,	816
-	aca Thr								-		-		-		-	į	864
	aat Asn 290							-							_	!	912
	ttg Leu															!	960

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 tgg cta att cca gga caa gag cag gaa cat gtg gag tag . 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu * <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly 40 Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val 75 Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 100 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 125 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 150 155 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 200 205

Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala

Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

220

225					230					235					240		
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Val 250	Pro	Asn	Ile	Leu	Leu 255	Phe		
Gln	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265		His	Thr	Asp 、	Arg 270	Thr	Leu		
G1u	Thr	Leu 275		Ile	Phe	Ile	Phe 280	Asn	Gln	Thr	Gly	Ile 285	Glu	Ala	Lys		
Lys	Asn 290	Val	۷al	Val	Thr	G1n 295	Ala	Asp	Gln	Ile	G1y 300	Pro	Leu	Pro	Ser		
Thr 305		Ile	Lys	Ser	Val 310	Asp	Trp	Leu	Leu	Val 315	Phe	Ser	Leu	Phe	Phe 320	•	
Leu	Ile	Ser	Phe	Ile 325	Met	Tyr	Ala	Thr	Ile 330	Arg	Thr	Glu	Ser	Ile 335	Arg		
Trp	Leu	Ile	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu						
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						gga Gly						-			-		96
						aaa Lys											144
						ggc Gly 55										-	192
						gtg Val											240

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65					70					75					80	
						-								gaa Glu 95	-	288
														att Ile		336
														ttc Phe		384
														atc Ile		432
	ctg Leu		tga *													444
	· <2	210> 211> 212> 213>	147	sar	oiens	5										
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Met 1	Ala	Phe	Pro	Lys 5	Lys	Lys	Leu	GIN	10	Leu	Val	Ala	Ala	Thr 15	He	
Thr	Pro	Met	Thr 20	Glu	Asn	Gly	Glu	I1e 25	Asn	Phe	Ser	Val	Ile 30	Gly	Gln	
Tyr	Val	Asp 35		Leu	Val	Lys	Glu 40		Gly	Val	Lys	Asn 45		Phe	Val	
Asn	Gly 50		Thr	Gly	Glu	Gly 55		Ser	Leu	Ser	Va1 60		Glu	Arg	Arg	
G1n 65		Ala	Glu	Glu	Trp 70		Thr	Lys	Gly	Lys 75		Lys	Leu	Asp	G1n 80	
	Ile	Пе	His	Va1 85		Ala	Leu	Ser	Leu 90		Glu	Ser	Gln	Glu 95		
Ala	Gln	His	Ala 100		G1u	Ile	Gly	Ala 105		Gly	Пе	Ala	Val 110	Ile	Ala	
Pro	Phe	Phe		Lys	Pro	Trp	Thr		Asp	Ile	Leu	Пe		Phe	Leu	

Glu 130 Leu		Ala	Ala	Ala	Pro 135	120 Leu	Pro	Cys	His	Phe 140	125 Ile	Thr	Ile	Thr	
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				gta Val									-	-	96
_	-			ttc Phe		-	-	-	-	_	_			-	144
				gtg Val				-							192
				ctt Leu 70											240
				gga Gly		_					-		_		288

													aag Lys		336
													atg Met		. 384
													aaa Lys		432
													acg Thr		480
													999 Gly 175	-	528
	-	_	-	-	-		_			-	-	-	gat Asp		576
													tct Ser		624
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<210> 201

<211> 885

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<213> Homo sapiens

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<221> CDS

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	cgc Arg								528
	cat His 180								576
	act Thr								624
	ttg Leu								672
	gtg Val								720
	aaa Lys								768
	tac Tyr 260								816
Пe	atg Met		Gln						864
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<211> 294

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290

Glu Lys Thr Gly His Lys

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280

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		-	_			_	tgg Trp	_			-				144
		-					gaa Glu		-	-	-	-	_		192
							aga Arg								240
							gtc Val 90							i	288
							ttg Leu							;	336
							aga Arg							;	384
	_			_			 gaa Glu							4	432

	130				135					140					
-		-	_								gtg Val	_	~		480
	_	_		_							ttc Phe				528
				-			_	-	_		gac Asp			-	576
_	-						_				gct Ala 205			_	624
											cca Pro				672
		 _					-			_	ata Ile		_	_	720
		_			_	~					gct Ala	-	~~	•	768
	_			•				-	-	_	aga Arg			~	816
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<210> 205

<211> 561

<212> DNA

<213> Homo sapiens

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His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser

cag gtg ctc cct gtg ttg aaa gag aat gtg gaa ggt cat gat tta cct 528 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 gca tot gag aaa cac cag gat gtt acc toc taa 561 Ala Ser Glu Lys His Gln Asp Val Thr Ser * 180 185 <210> 206 <211> 186 <212> PRT <213> Homo sapiens <400> 206 Met Ile His Trp His Ser Glu Lys Ala Thr Leu Leu Leu Asn Ala Pro 10 Ser Phe Ser Asp Gln Leu Pro Gly Thr Met Ala Thr Leu Ser Leu Val Asn Glu Ala Gln Tyr Leu Leu Ile Asn Thr Ser Ser Ile Leu Glu Leu 40 His Arg Gln Leu Asn Thr Ser Asp Glu Asn Gly Lys Glu Glu Leu Phe 55 Ser Leu Lys Asp Leu Ser Leu Arg Phe Arg Ala Asn Ile Ile Asn 70 75 Gly Lys Arg Ala Phe Glu Glu Glu Lys Trp Asp Glu Ile Ser Ile Gly Ser Leu Arg Phe Gln Val Leu Gly Pro Cys His Arg Cys Gln Met Ile 105 Cys Ile Asp Gln Gln Thr Gly Gln Arg Asn Gln His Val Phe Gln Lys 120 125 Leu Ser Glu Ser Arg Glu Thr Lys Val Asn Phe Gly Met Tyr Leu Met 135 140 His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser 150 155 Gin Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 170 175 Ala Ser Glu Lys His Gln Asp Val Thr Ser 180 <210> 207 <211> 1272 <212> DNA <213> Homo sapiens

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							cgg Arg									192
					-		cgc Arg	_		_		_				240
•							999 Gly							_		288
Tyr	Lys	Asp	Tyr	Пe	Thr	Phe	att Ile 105	Glu	Gly		Ser	Tyr	His			336
							gaa Glu									384
							gtt Val									432

130				135				140				
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			cat His									528
			atc Ile									576
			gct Ala									624
-		-	gaa Glu									672
			caa G1n 230									720
			att Ile									768
		Ser	ttc Phe									816
			gta Val									864
 	-		tta Leu	-	-	-	_	-				912
		_	cct Pro			_			-	-		960

305					310					315.					320	
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-										ttt Phe						1056
		-							_	tta Leu			-			1104
				-	-	-				gaa Glu			-			1152
			_		-	-		-		tct Ser 395	_		_		_	1200
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Phe	Ser	G1 <i>y</i> 35	Pro	Met	Met	Пe	Ile 40	Thr	Gln	Lys	Ile	Thr 45	Ser	Leu	Ala
Cys	G7u 50	Ile	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	G1u 60	Glu	Leu	Thr	Ser
Ser 65	Gln	Arg	Asp	Leu	Ala 70	Val	Arg	Arg	Met	Pro 75	Ser	Leu	Leu	Glu	Tyr 80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	11e 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
Ser	Tyr	Lys	Asp 100	Tyr	Пe	Thr	Phe	Ile 105	Glu	Gly	Arg	Ser	Tyr 110	His	Πe
Thr	Gln	Ser 115	Gly	Glu	Asn	Gly	Lys 120	Glu	Glu	Thr	Gln	Tyr 125	Glu	Arg	Thr
Glu	Pro 130	Ser	Pro	Asn	Thr	Ala 135	Val	Val	G1n	Lys	Leu 140	Leu	Val	Cys	Gly
Leu 145	Ser	Leu	Leu	Phe	His 150	Leu	Thr	Ile	Cys	Thr 155	Thr	Leu	Pro	Val	Glu 160
Tyr	Asn	Ile	Asp	GTu 165	His	Phe	Gln	Ala	Thr 170	Ala	Ser	Trp	Pro	Thr 175	Lys
Ile	Ile	Tyr	Leu 180	Tyr	Ile	Ser	Leu	Leu 185	Ala	Ala	Arg	Pro	Lys 190	Tyr	Tyr
Phe	Ala	Trp 195	Thr	Leu	Ala	Asp	Ala 200	Ile	Asn	Asn	Ala	Ala 205	Gly	Phe	Gly
	210	-		·		215	-				220	,	Leu		
Asn 225	Leu	Arg	Ile	Gln	G1n 230	Ile	Glu	Met	Ser	Thr 235	Ser	Phe	Lys	Met	Phe 240
Leu	Asp	Asn	Trp	Asn 245	Ile	G1n	Thr	Ala	Leu 250	Trp	Leu	Lys	Arg	Va1 255	Cys
_		•	260					265					Ile 270		
Ala	Пe	Trp 275	His	Gly	Val	Tyr	Pro 280	Gly	Tyr	Tyr	Leu	Thr 285	Phe	Leu	Thr
Gly	Va1 290	Leu	Met	Thr	Leu	Ala 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn	Phe	Arg
His 305	Tyr	Phe	lle	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	11e 320
Thr	Trp	Ile	Val	Thr 325	G1n	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340	Пе	Lys	Pro	Ser	Leu 345	Thr	Phe	Tyr	Ser	Ser 350	Trp	Tyr
Tyr	Cys	Leu 355	His	He	Leu	Gly	11e	Leu	Val	Leu	Leu	Leu 365	Leu	Pro	Val

Lys	Lys 370	Thr	Gln	Arg	Arg	Lys 375	Asn	Thr	His	Glu	Asn 380	Пe	Gln	Leu	Ser	
G1n 385	Ser	Lys	Lys	Phe	Asp 390	Glu	Gly	Glu	Asn	Ser 395	Leu	Gly	Gln	Asn	Ser 400	
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											agc Ser		-	-		144
		_	-		-	_			-		gga Gly 60	-				192
											gcc Ala					240
											gac Asp					288
gtg	ctg	acc	agc	ctt	gtg	gcg	ctg	cgg	cgg	gag	gtg	gag	gag	ctg	aga	336

Val	Leu	Thr	Ser 100	Leu	Val	Ala	Leu	Arg 105	Arg	Glu	Va1	Glu	Glu 110	Leu	Arg	
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	atg Met 130	-			_	_	-							-		432
	cgg Arg															480
-	tcc Ser	-		-	-			-	-		-	_				528
	aca Thr	-					_				-		-		_	576
	gag Glu															624
	aag Lys 210	-			-	-		-						-		672
-	gcc Ala	_		-	~ ~					_		-	-	_		720
	ctg Leu					-	-								_	768
	gag Glu			_		_				-					_	816
aa	caq	gac	ttt	ct.c	taa	cac	cta	acc	cga	acc	tac	aqt.	gac	ata	tat	864

	Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys	
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		_	_	•		_	~	-		-		_		•	gct Ala	•	960
															cat His 335		1008
															cat His		1056
															ttt Phe		1104
															gaa Glu		1152
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															gga Gly 415		1248
,															cta Leu		1296
				-					_						ctg Leu		1344
	gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

WO 01/29221 PCT/US00/29052

297

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Arg Gln Asp Phe Leu Trp Arg Leu Ala Arg Ala Tyr Ser Asp Met Cys
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Glu Leu Thr Glu Glu Val Ser Glu Lys Lys Ser Tyr Ala Leu Asp Gly
Lys Glu Glu Ala Glu Ala Ala Leu Glu Lys Gly Asp Glu Ser Ala Asp
                                        315
                    310
Cys His Leu Trp Tyr Ala Val Leu Cys Gly Gln Leu Ala Glu His Glu
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                                    330
Ser Ile Gln Arg Arg Ile Gln Ser Gly Phe Ser Phe Lys Glu His Val
                                345
Asp Lys Ala Ile Ala Leu Gln Pro Glu Asn Pro Met Ala His Phe Leu
                            360
                                                 365
Leu Gly Arg Trp Cys Tyr Gln Val Ser His Leu Ser Trp Leu Glu Lys
                        375
Lys Thr Ala Thr Ala Leu Leu Glu Ser Pro Leu Ser Ala Thr Val Glu
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Asp Ala Leu Gln Ser Phe Leu Lys Ala Glu Glu Leu Gln Pro Gly Phe
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Ser Lys Ala Gly Arg Val Tyr Ile Ser Lys Cys Tyr Arg Glu Leu Gly
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Lys Asn Ser Glu Ala Arg Trp Trp Met Lys Leu Ala Leu Glu Leu Pro
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				-							att Ile		96
											cgg Arg	-	144
	-				-				_	_	atg Met	_	192
											ccg Pro		240
											aac Asn 95		288
	-	-		_	-					-	cgc Arg		336
 _		 		-	-	_		-		_	gcc Ala		384
				-							ttc Phe		432
		Glu	-	Asp	Arg						ttg Leu	_	480
											tgt Cys 175		528
		-		•	-		_				gtg Val	-	576

		_		_		_	ctc Leu 200	_						-		624
-			_				agg Arg					_			-	672
							ttc Phe									720
		-					aaa Lys									768
			_	-	•		cct Pro	-	_	-	-		-	_	-	816
			-				gag G1u 280									864
							gag Glu									912
							ctg Leu					-				960
							agc Ser	Met		Arg					-	1008
-	_	_	-				gtc Val				_				gtt Val	1056
							gaa Glu 360									1104

aac tot gac agc aag cag aaa otg aat gac tga 1137 Asn Ser Asp Ser Lys Gin Lys Leu Asn Asp * 370 <210> 212 <211> 378 <212> PRT <213> Homo sapiens <400> 212 Met Asp Leu Ala Gly Leu Leu Lys Ser Gln Phe Leu Cys His Leu Val 10 Phe Cys Tyr Val Phe Ile Ala Ser Gly Leu Ile Ile Asn Thr Ile Gln Leu Phe Thr Leu Leu Leu Trp Pro Ile Asn Lys Gln Leu Phe Arg Lys Ile Asn Cys Arg Leu Ser Tyr Cys Ile Ser Ser Gln Leu Val Met Leu 55 Leu Glu Trp Trp Ser Gly Thr Glu Cys Thr Ile Phe Thr Asp Pro Arg 75 Ala Tyr Leu Lys Tyr Gly Lys Glu Asn Ala Ile Val Val Leu Asn His 90 Lys Phe Glu Ile Asp Phe Leu Cys Gly Trp Ser Leu Ser Glu Arg Phe 105 Gly Leu Leu Gly Gly Ser Lys Val Leu Ala Lys Lys Glu Leu Ala Tyr 120 Val Pro Ile Ile Gly Trp Met Trp Tyr Phe Thr Glu Met Val Phe Cys 130 135 140 Ser Arg Lys Trp Glu Gln Asp Arg Lys Thr Val Ala Thr Ser Leu Gln 150 155 His Leu Arg Asp Tyr Pro Glu Lys Tyr Phe Phe Leu Ile His Cys Glu 170 Gly Thr Arg Phe Thr Glu Lys Lys His Glu Ile Ser Met Gln Val Ala 185 Arg Ala Lys Gly Leu Pro Arg Leu Lys His His Leu Leu Pro Arg Thr 200 Lys Gly Phe Ala Ile Thr Val Arg Ser Leu Arg Asn Val Val Ser Ala 220 215 Val Tyr Asp Cys Thr Leu Asn Phe Arg Asn Asn Glu Asn Pro Thr Leu 230 235 Leu Gly Val Leu Asn Gly Lys Lys Tyr His Ala Asp Leu Tyr Val Arg 245 250 255

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Tyr	Arg 290	Thr	Gly	Thr	Phe	Pro 295		Thr	Pro _.	Met	Val 300		Pro	Arg	Arg	
Pro 305		Thr	Leu	Val	Asn 310		Leu	Phe	Trp	Ala 315	Ser	Leu	Val	Leu	Tyr 320	
Pro	Phe	Phe	Gln	Phe 325	Leu	Val	Ser	Met	Ile 330	Arg	Ser	Gly	Ser	Ser 335	Leu	
Thr	Leu	Ala	Ser 340	Phe	Ile	Leu	Val	Phe 345	Phe	Val	Ala	Ser	Val 350	Gly	Val	
Arg	Trp	Met 355	Ile	Gly	Val	Thr	G1u 360	Ile	Asp	Lys	Gly	Ser 365	Ala	Tyr	Gly	
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											agc Ser					144
-						_					cag Gln 60	_	-	~		192 ·
ссс	agc	aac	acc	cct	gcc	acg	ccg	ССС	aac	ttc	ССС	gat	gcg	ctg	gcc	240

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										ctg Leu						288
										gca Ala						336
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										aaa Lys 155						480
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Met	Phe	Ser	Lys	Leu 85	Arg	Ala	Ser	Glu	Gly 90	Leu	Gln	Ser	Ser	Asn 95	Ser	
Pro	Met	Thr	Ala 100	Ala	Ala	Cys	Ser	Pro 105	Pro	Ala	Asn	Phe	Ser 110		Phe	
		115					120		•		Trp	125				
Ser	Pro 130	Thr	Thr	Phe	His	His 135	Leu	His	Arg	Pro	Gln 140	Pro	Thr	Trp	Pro	
145				Gln	Gly 150	Gly	Ala	Gln	Gln	Lys 155	Ala	Met	Ala	Ala	Met 160	
Asp	Ģly	Gln	Arg													
	<'a	212>	215 3105 DNA Homo		oiens	5										
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											atc Ile			_		96
											gtc Val					144
											gga Gly 60					192
											aac Asn	-				240
aaa	ggc	aaa	ggt	aaa	aaa	cat	gaa	gca	gat	gag	ttg	agt	gga	gat	gct	288

Lys	Gly	Lys	Gly	Lys 85		His	Glu	Ala	Asp 90		Leu	Ser	Gly	Asp 95	Ala	
			gat Asp 100													336
			gag Glu													384
			aat Asn													432
			aac Asn													480
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			gat Asp 180													576
gaa Glu	aat Asn	gag Glu 195	aaa Lys	gat Asp	ata Ile	gca Ala	ggt G1y 200	tct Ser	ggt Gly	gat Asp	ggt Gly	aca Thr 205	caa Gln	gaa Glu	gta Val	624
			ctt Leu													672
			gag Glu						Thr							720
			tcg Ser					Ala								768
ttt	gat	ggt	gat	gac	ctc	cta	gaa	aca	ggt	aaa	aat	gtg	aaa	att	aca	816

Phe	Asp	Gly	Asp 260	Asp	Leu	Leu	Glu	Thr 265	G1y	Lys	Asn	Val	Lys 270	Ile	Thr	
				-	aag Lys			_		-	,	-		•	_	864
					agc Ser											912
					gac Asp 310							-		_	-	960
					aag Lys											1008
					ccc Pro											1056
					tct Ser										_	1104
					agt Ser											1152
			-	-	gga Gly 390							~	•	_	_	1200
			Phe		aaa Lys											1248
		Ala			cct Pro		Ala									1296
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Ser	Ser	Ser 435	Thr	Glu	Val	Ser	Arg 440	Cys	Ile	Ala	His	Leu 445	His	Arg	Thr	
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									gat Asp							1440
							_		gat Asp 490	-	-	-	_			1488
		-			-			_	tcg Ser					_		1536
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									gaa Glu	-				_	-	1632
									cca Pro							1680
									cca Pro 570		-			-		1728
									aag Lys							1776
	Lys				-	Tyr	-		aaa Lys		Пe				•	1824
aag	atg	aag	gaa	caa	agg	ttg	aga	gaa	cat	tta	gtt	cgt	ttt	gaa	agg	1872

Lys	Met 610	Lys	Glu	Gln	Arg	Leu 615	Arg	Glu	His	Leu	Va1 620	Arg	Phe	Glu	Arg	
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		_		_	Glu	cgc Arg					_	_		-	-	1968
	-	-		_	_	gag Glu	-				-		-			2016
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			-		-	agg Arg			-	-		-		-		2160
						aaa Lys						•			-	2208
						gag Glu			_	-			_		-	2256
						tcc Ser	-			-				-		2304
						gag Glu 775										2352
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_		_						-	_		-	aga Arg					2496
												cga Arg		-	-		2544
				-		-	_	-				gac Asp 860			_		2592
T												aat Asn					2640
					-	-		-				gac Asp					2688
						-	-					gta Val				-	2736
	-		_	_								gct Ala	-				2784
	er				-							cga Arg 940					2832
	n						-			-	-	cgc Arg				_	2880
ac	a	agc	gga	сса	agg	aaa	gag	tgg	cat	ggt	сса	ccc	tct	caa	ggg	cct	2928

Thr	Ser	Gly	Pro	Arg 965	Lys	Glu	Trp	His	Gly 970	Pro	Pro	Ser	Gln	Gly 975	Pro		
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	ata Ile		Gln			-		Ala					Arg		-	30	24
	atc Ile 101	Ser					Pro					Ser			_	30	72
	ttt Phe 5					Pro				tga *						31	05
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Ala	Glu	Gly	Lys 20	Lys	Ile	Thr	Asp	Leu 25	Arg	Val	Ile	Asp	Leu 30	Lys	Ser		
G1u	Leu	Lys 35	Arg	Arg	Asn	Leu	Asp 40	Ile	Thr	Gly	Val	Lys 45	Thr	Val	Leu		
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Leu	Leu 210	Ser	Asp	Glu	Asp	Cys 215	Met	Ser	Val	Pro	Gly 220	Lys	Thr	His	Arg	
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	370					375					380		Thr	•	
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	-			gtc Val		-			-			•		576
				tac Tyr			_	-			-			624
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				ttt Phe 230	_	-		-				_	_	720

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	gga Gly 290	-			_		_			-			-			912
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	gaa Glu															1056
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Cys	Ser	Ser	Val 100	Asp	Phe	Ser	Val	Phe 105	Ser	Ala	Cys	Ser	Val 110	Pro	Val	
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Ala	Leu	Ser	Phe	Ile 165	Asn	Pro	Glu	Val	Pro 170	Asp	Glu	Asn	Asn	Phe 175	Asp	
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Val	Ser	Phe 195		Thr	Lys	Leu	Asp 200		Pro	Thr	Ala	Ala 205		Tyr	G1u	
Tyr	Gly 210		Pro	Leu	Gln	Thr 215		Asp	Ser	Phe	Leu 220		Phe	Pro	Ser	

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Glu	Glu	Пе	G1u 260	Ala	Leu	Ser	Met	A1a 265	Phe	Tyr	Ser	Ser	Pro 270	Glu	Πe
Leu	Arg	Va1 275	Pro	Asp	Ser	Arg	Lys 280	Lys	Val	Pro	Пе	Thr 285	Val	Gln	Ser
He	Val 290	Ile	Gln	Ser	Leu	Asn 295	Lys	Thr	Leu	Thr	Arg 300	Arg	Glu	Asp	Thr
Asp 305	۷a٦	Leu	G1n	Pro	Thr 310	Leu	Val	Asn	Ala	Gly 315	His	Phe	Ser	Leu	Cys 320
Val	Asn	Val	Val	Leu 325	Glu	Val	Lys	Tyr	Ser 330	Leu	Thr	Tyr	Thr	Asp 335	ΑTa
Gly	Glu	Val	Thr 340	Lys	Ala	Asp	Leu	Ser 345	Phe	Val	Leu	Gly	Thr 350	Val	Ser
		355			Leu		360	-				365			
	370				Val	375			•		380	•	•		
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Пe	Gln	Thr	Thr	Asn 405	Arg	Tyr	Gly	Gln ·	Leu 410	Thr	Ile	Leu	His	Ser 415	Thr
			420		Leu			425	-				430		
		435			Gln		440	-				445			
	450				Val	455		-			460			·	·
465				·	Tyr 470					475					480
-			·	485	Val				490					495	
Arg	Lys	Asp	Ser 500	Cys	Gln	Leu	Pro	G1y 505	Ala	Leu	Val	Ile	G1u 510	Val	Lys
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Ser	Ala	Pro	Ala	G1u 565	Ala	Gly	Phe	Arg	A1a 570	Pro	Pro	Ala	Ile	Asn 575	Ala

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gtg Val 145	Ser	cto Leu	aat Asr	gca Ala	tgg Trp 150	Phe	tgg Trp	tcc Ser	aca Thr	gto Val	Phe	cad His	acc Thr	agg Arg	gac Asp 160	480
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gtg Val	cac His 210	gtc Val	tcc Ser	tac Tyr	ctg Leu	agc Ser 215	ctc Leu	atc Ile	cgc Arg	ttc Phe	gac Asp 220	tat Tyr	ggc Gly	tac Tyr	aac Asn	672
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gcc Ala	tgg Trp	tgc Cys	ctg Leu	tgg Trp 245	aac Asn	cag G1n	cgg Arg	cgg Arg	ctg Leu 250	cct Pro	cac His	gtg Val	cgc Arg	aag Lys 255	tgc Cys	768
gtg Val	gtg Val	gtg Val	gtc Val 260	ttg Leu	ctg Leu	ctg Leu	cag Gln	999 Gly 265	ctg Leu	tcc Ser	ctg Leu	ctc Leu	gag Glu 270	ctg Leu	ctt Leu	816
gac Asp	Phe	cca Pro 275	ccg Pro	ctc Leu	ttc Phe	Trp	gtc Val 280	ctg Leu	gat Asp	gcc Ala	cat His	gcc Ala 285	atc Ile	tgg Trp	cac His	864
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ga Ası 30!	s agc Ser	ctg Leu	tac Tyr	ctg Leu	ctg Leu 310	aag Lys	gaa Glu	tca Ser	gag Glu	gac Asp 315	aag Lys	ttc Phe	aag Lys	ctg Leu	gac Asp 320	!	960
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Let 225	ı Val	A1 a	a Asr	ı Val	A1 a		e Gly	/ Leu	ı Val	1 Asr 235		Va	Trp	) Trp	Leu 240	
Ala	Trp	Cys	Leu	Trp 245		G]r	Arc	j Arg	Leu 250	ı Pro		, Val	Arg	Lys 255	Cys	
Val	Val	۷a٦	Va1 260		. Leu	l Leu	G]r	Gly 265		ı _. Ser	· Leu	ı Lei	Glu 270	r Leu	Leu	
		275	·				280	)				285	)	·	His	
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Asp 305	Şer	Leu	Tyr	Leu	Leu 310		Glu	Ser	Glu	Asp 315		Phe	Lys	Leu	Asp 320	
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											ccg Pro					144
											cgc Arg 60					192
tg	cag	ctg	ctc	ggc	cgc	ctc	cca	ctc	ttc	qqc	cta	ggc	cac	cta	atc	240

Leu 65		Leu	Leu	Gly	Arg 70	Leu	Pro	Leu	Phe	Gly 75		Gly	Arg	Leu	Va1 80	
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ctc Leu	acg Thr	cgg Arg	gtg Val 100	cgg Arg	ccc Pro	gac Asp	tac Tyr	acg Thr 105	gcg Ala	cag Gln	aac Asn	ttg Leu	gac Asp 110	cac His	999 Gly	336
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cgg Arg	gag Glu 130	atc Ile	gaa Glu	cac His	gtc Val	atg Met 135	tac Tyr	cat His	gac Asp	tgg Trp	cgg Arg 140	ctg Leu	gtg Val	ccc Pro	aag Lys	432
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Leu Gin Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
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                                    90
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
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Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
                            120
                                                125
Arg Glu Ile Glu His Val Met Tyr His Asp Trp Arg Leu Val Pro Lys
                        135
His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
                                        155
Leu Ala Ser Val Pro Tyr Pro Pro Leu Leu Arg Ala Met Ile Ile Ala
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                                    170
Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
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aca Thr	gag Glu	990 Gly	cat His	Cys	cct Pro	: cgg Arg	cag Gln	caç Glr 185	ı Trp	gco Ala	cto Leu	g gtg ı Val	gag Glu 190	Phe	gag Glu	576
aag Lys	ccc Pro	gto Val 195	Thr	tgc Cys	cct Pro	. cgg Arg	ctg Leu 200	Cys	ctg Leu	gtg Val	ı att Ile	ggc Gly 205	Ser	agg Arg	cta Leu	624
gat Asp	gcg Ala 210	Asp	att Ile	cac	acc Thr	aac Asn 215	Thr	tgc Cys	cgg Arg	cta Leu	gcc Ala 220	ttc Phe	cat His	ggc Gly	atc Ile	672
ctg Leu 225	Leu	cac His	999 Gly	cta Leu	gag Glu 230	gac Asp	agg Arg	aac Asn	tac Tyr	gcc Ala 235	gac Asp	agc Ser	ttc Phe	ctg Leu	ccc Pro 240	720
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gcg Ala	atg Met	gat Asp	gac Asp 260	tac Tyr	agt Ser	gtg Val	atc Ile	ggc Gly 265	.cgc Arg	tcc Ser	ctg Leu	ttc Phe	aaa Lys 270	aag Lys	gaa Glu	816
acc Thr	aac Asn	atc Ile 275	cag Gln	ctc Leu	ttc Phe	gtg Val	ggg Gly 280	ctc Leu	aag Lys	gtg Val	cac His	ttg Leu 285	tcc Ser	act Thr	999 Gly	864
gaa Glu	ctg Leu 290	ggc Gly	atc Ile	atc Ile	gac Asp	agt Ser 295	gcc Ala	ttc Phe	ggc Gly	cag Gln	agc Ser 300	ggc Gly	aag Lys	ttc Phe	aag Lys	912
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325 330 335 cag gag gag agc gcc gag cgg agn agg ccc tca cag cat gtg gtg ctc 1056 Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu 340 345 age ctg act ttc aag cgt tat gtc ttc gac acc cac aag cgc atg gtt 1104 Ser Leu Thr Phe Lys Arg Tyr Val Phe Asp Thr His Lys Arg Met Val 355 360 cag tct ccc tga 1116 Gln Ser Pro * 370 <210> 232 <211> 371 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(371) <223> Xaa = Any Amino Acid <400> 232 Met Ser Val Ala His Cys Phe Ser Ile Lys Gly Gln Gly Thr Val Met Thr Gly Thr Ile Leu Ser Gly Ser Ile Ser Leu Gly Asp Ser Val Glu Ile Pro Ala Leu Lys Val Val Lys Lys Val Lys Ser Met Gln Met Phe His Met Pro Ile Thr Ser Ala Met Gln Gly Asp Arg Leu Gly Ile Cys 55 Val Thr Gln Phe Asp Pro Lys Leu Leu Glu Arg Gly Leu Val Cys Ala Pro Glu Ser Leu His Thr Val His Ala Ala Leu Ile Ser Val Glu Lys 90 Ile Pro Tyr Phe Arg Gly Pro Leu Gln Thr Lys Ala Lys Phe His Ile 105 Thr Val Gly His Glu Thr Val Met Gly Arg Leu Met Phe Phe Ser Pro 120 125 Ala Pro Asp Asn Phe Asp Gln Glu Pro Ile Leu Asp Ser Phe Asn Phe 130 135 140

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Ser Gln Glu Tyr Leu Phe Gln Glu Gln Tyr Leu Ser Lys Asp Leu Thr
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Pro Ala Val Thr Asp Asn Asp Glu Ala Asp Lys Lys Ala Gly Gln Ala
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Thr Glu Gly His Cys Pro Arg Gln Gln Trp Ala Leu Val Glu Phe Glu
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Lys Pro Val Thr Cys Pro Arg Leu Cys Leu Val Ile Gly Ser Arg Leu
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Asp Ala Asp Ile His Thr Asn Thr Cys Arg Leu Ala Phe His Gly Ile
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Leu Leu His Gly Leu Glu Asp Arg Asn Tyr Ala Asp Ser Phe Leu Pro
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Arg Leu Lys Val Tyr Lys Leu Lys His Lys His Gly Leu Val Glu Arg
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                                    250
Ala Met Asp Asp Tyr Ser Val Ile Gly Arg Ser Leu Phe Lys Lys Glu
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Thr Asn Ile Gln Leu Phe Val Gly Leu Lys Val His Leu Ser Thr Gly
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Glu Leu Gly Ile Ile Asp Ser Ala Phe Gly Gln Ser Gly Lys Phe Lys
                        295
Ile His Ile Pro Gly Gly Leu Ser Pro Glu Ser Lys Lys Ile Leu Thr
                    310
Pro Ala Leu Lys Lys Arg Ala Arg Ala Gly Arg Gly Glu Ala Thr Arg
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Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu
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				cga Arg								Leu				192
acc Thr 65	ggg G1y	ctc Leu	cca Pro	gcc Ala	cta Leu 70	gac Asp	cag Gln	ctc Leu	tta Leu	ggt Gly 75	gga Gly	ggt Gly	tta Leu	gcc Ala	gtt Val 80	240
				cta Leu 85												288
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	tct Ser 210	Ser														672	
	aag Lys										Tyr					720	
	gga Gly															768	
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	aat Asn															864	
	ggt Gly 290															912	
	cat His															960	
	gat Asp		Val					Ser								1008	
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Ile	Ala 50		Thr	Arg	Pro			Arg	Asn	Gly	Gln 60		Leu	Val	Ser		
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Ala	Trp	Arg	Tyr	Gln 165	Leu	Leu	Pro	Lys	Met 170		Ile	Gly	Pro	Val 175	Ser
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			340		Lys			345					350		
		355			Asn		360					365		-	•
	370				Lys	375	-				380				
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					gag Glu											192
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					cat His											336
					aag Lys											384
atg 1et	gcg Ala	gac Asp	ctc Leu	cta Leu	cag G1n	cag G1n	ggt Gly	cct Pro	gat Asp	gtg Val	gca Ala	ccc Pro	agc Ser	ttc Phe	ctc Leu	432

130			135					140				
Ser					tgg Trp			Ser				480
					gct Ala							528
			-	-	tgt Cys 185	_		_		-	_	57€
		-			atg Met				_			624
					acc Thr			-		_	 _	672
					ctg Leu							720
					cta Leu							768
			-		gca Ala 265		-			_	 •	816
					gag Glu							864
					cta Leu						-	912
					ggc Gly							960

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cgg Arg	aag Lys	cgc Arg	tto Phe	tcc Ser 325	Leu	cag G1n	ago Ser	tat Tyr	9cg Ala 330	Asp	tat Tyr	ato Ile	agt Ser	gcc A1a 335	gat Asp		1008	
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cca Pro	tct Ser 370	gct Ala	atg Met	ccc Pro	acc Thr	cca Pro 375	tct Ser	ctg Leu	ctg Leu	tgt Cys	tcc Ser 380	agc Ser	cct Pro	gtg Val	gcc Ala		1152	
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Mot		<004		Dna	Clu	T	Clu	C3	Tha	1	Thus	۸	1	A 7				
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Ile	Leu	Ala	Lys 20	His	Phe	Ala	Asp	A1a 25	Arg	He	Val	Gly	Thr 30	Asp	Пе			
Arg	Asp	Ser 35	Leu	Met	Gln	Ala	Leu 40		Ser	Tyr	Val	Cys 45		Pro	His			
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	Trp	Ile	Leu	Va1 85		Leu	Trp	Arg	Gly 90		Gly	Phe	Gly	-				
Tyr	Thr	Arg	Leu 100		His	Leu	Leu			Lys	Leu	Glu		95 Ala	Asn			
Leu	Pro	Ser		Gln	Lys	Pro	Cys	105 Pro	Ser	Thr	Leu.	Leu	110 Gln	Gln	His			

		115					120					125			
Met	Ala		Leu	Leu	Gln	Gln			Asp	Val	Ala			Phe	Leu
	130					135					140				
Asn 145		Val	Leu	Asn	61n 150	Leu	Asn	Trp	Ala	Phe 155		Glu	Phe	Ile	Gly 160
Met	Ile	Gln	Glu	Ile 165	Gln	Gln	Ala	Ala	G1u 170	Arg	Leu	Glu	Arg	Asn 175	
Val	Asp	Ser	Arg 180			Lys	Val	Cys 185		Thr	Cys	Phe	Asp 190		Ser
Val	Ser	Leu 195	Leu	Arg	۷a٦	Leu	G1u 200		Thr	Ile	Thr	Leu 205		Pro	Glu
Ile	Phe 210		Asp	Trp	.Thr	Arg 215		Thr	Ser	Glu	Met 220		Leu	Arg	Arg
Leu 225		Gln	Leu	Leu	Asn 230		Val	Leu	Asn	Arg 235		Thr	Ala	Glu	Arg 240
	Leu	Phe	Asp	Arg 245		۷al	Thr	Leu	Arg 250		Pro	Gly	Leu	G1u 255	
Val	Asp	His	Tyr 260		Пe	Leu	Val	A1a 265		Thr	Gly	Ile	Leu 270		Gln
Leu	Leu	Val 275	Arg	Gly	Pro	Ala	Ser 280		Arg	Glu	Gln	A1a 285		Ser	Val
Leu	Leu 290	Ala	Asp	Pro	Cys	Phe 295		Leu	Arg	Ser	Ile 300		Tyr	Leu	Leu
G1y 305	Gln	Pro	Glu	Pro	Pro 310	Ala	Pro	Gly	Thr	Ala 315		Pro	Ala	Pro	Asp 320
Arg	Lys	Arg	Phe	Ser 325	Leu	G1n	Ser	Tyr	A1 a 330	Asp	Tyr	Пe	Ser	Ala 335	
G1u	Leu	Ala	G1n 340	Val	Glu	Gln	Met	Leu 345	Ala	His	Leu	Thr	Ser 350	Ala	Ser
Ala	Gln	A1a 355	Ala	Ala	Ala	Ser	Leu 360	Pro	Thr	Ser	Glu	G1u 365	Asp	Ser	Ala
Pro	Ser 370	Ala	Met	Pro	Thr	Pro 375	Ser	Leu	Leu	Cys	Ser 380	Ser	Pro	Val	Ala
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145				150				155					160	
							gca Ala 170						-	528
							cgg Arg							576
		Ser					gcc Ala				-	-		624
	Thr					_	aat Asn					~ ~		672
							gta Val							720
							cct Pro 250	-	-		_	~ ~		768
							ata Ile							816
		-			_	-	ttg Leu	-	-	_			aaa Lys	864
							tcc Ser		-			~		912
			Gly				atg Met							960
							tat Tyr							1008

325 330 335 agt ggt aaa tgc cct ctt cca agg caa caa gta aca gaa att ata ttt 1056 Ser Gly Lys Cys Pro Leu Pro Arg Gln Gln Val Thr Glu Ile Ile Phe 340 345 gtt tta aaa gca gtc agt act ctt att gat tca ctt aag aaa act cag 1104 Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys Thr Gln 355 cct gag aat gtt gat gga aat acc tgg gca caa gta att gcc tta tac 1152 Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala Leu Tyr 370 375 380 cca act tta gta gaa tgc atc acc tgt tct tct tca gaa gtc tgt tct 1200 Pro Thr Leu Val Glu Cys Ile Thr Cys Ser Ser Ser Glu Val Cys Ser 385 390 395 400 gca ctt aaa gag gca cta gtt cct ttt aag gat ttc atg cag cca cca 1248 Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe Met Gln Pro Pro 405 410 415 gca tcc aga gtt caa aat gga gaa tct tga 1278 Ala Ser Arg Val Gln Asn Gly Glu Ser * 420 425 <210> 238 <211> 425 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(425) <223> Xaa = Any Amino Acid <400> 238 Met Asp Asp Leu Gln Lys Leu Gly Val Ile Leu His Ser Ala Ile Ser 1 5 Val Pro Ile Ser Ser Asp Ala Ser Pro Phe Ile Leu Pro Ser Tyr Thr 25 Glu Ala Val Leu Thr Ser Leu Gln Glu Ala Val Leu Thr Ala Leu Asp 35 40 45

Val	Leu 50	Gln	Lys	Ala	Ile	Cys 55	Val	Gly	Pro	Glu	Asn 60	Met	Gln	Ile	Met
Tyr 65	Pro	Ala	Ile	Phe	Asp 70	Gln	Leu	Leu	A٦a	Phe 75	Val	Glu	Phe	Ser	Cys 80
Lys	Pro	Pro	Gln	Tyr 85	Gly	Gln	Xaa	Glu	Thr 90	Lys	His	Ile	Ala	Asn 95	Ala
Lys	Tyr	Asn	Gln 100	Пe	Gln	Leu	Phe	Ala 105	Pro	Ala	Glu	Trp	Val 110	Ala	Leu
Asn	Tyr	Val 115	Pro	Phe	Ala	Glu	Arg 120	Ser	Leu	Glu	Val	Val 125	Val	Asp	Leu
	130	-			Cys	135	_				140		·		
145					Thr 150					155					160
				165	Thr				170					175	
			180		Leu			185					190		
		195			Trp		200					205		·	
	210				He	215					220				
225					Ile 230					235					240
				245	Ala				250					255	
			260		Asn			265					270		
		275			Ile		280					285			
	290				Leu	295					300				
305					Tyr 310					315					320
-	,			325	Val			•	330					335	
			340		Leu			345					350		
Val	Leu	Lys 355	Ala	Val	Ser	Thr	Leu 360	Ile	Asp	Ser	Leu	Lys 365	Lys	Thr	Gln
	370				Gly	375		•			380				·
Pro 385	Thr	Leu	Val	Glu	Cys 390	Ile	Thr	Cys	Ser	Ser 395	Ser	Glu	Val	Cys	Ser 400

Ala	Leu	Lys	G1u	Ala 405	Leu	Val	Pro	Phe	Lys 410	Asp	Phe	Met	Glņ	Pro 415	Pro		
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				-		_		_	-	-	-			ctc Leu			192
						-		-	_	-				aac Asn			240
														ggt Gly 95		;	288
														aac Asn		;	336
tgg	ttg	gct	aaa	ggg	ctt	gga	gct	tgt	acc	tcc	agg	ССС	ata	cat	cct	;	384

Trp	Leu	Ala 115	Lys	Gly	Leu	Gly	Ala 120	Cys	Thr	Ser	Arg	Pro 125	Ile	His	Pro	
		_									cac His 140	_	_	-		432
						-					atg Met		-			480
						_					gct Ala					528
	-						_		_		cag Gln	~	•		•	576
											ctt Leu		_	-	-	624
				-		-		_			cat His 220			•		672
		-		-	-	•		-		_	gca Ala		_		-	720
											cgc Arg					768
											gtg Val					816
	Ser					Leu					gct Ala					864
aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	caa	gga	912

Thr	Gly 290	G1u	Met	Ser	His	His 295	Asp	Thr	Leu	Asp	A1a 300	Ala	Ser	Gln	Gly	
			atc Ile									-	-			960
			cga Arg	_	-	_	_						_			1008
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Ser	Phe	Ala	Glu 20	Ser	Trp	Asp	Asn	Va1 25	Gly	Leu	Leu	Val	Glu 30	Pro	Ser	
Pro	Pro	His 35	Thr	Val	Asn	Thr	Leu 40	Phe	Leu	Thr	Asn	Asp 45	Leu	Thr	Glu	
Glu	Va1 50	Met	Glu	Glu	Va]	Leu 55	Gln	Lys	Lys	Ala	Asp 60	Leu	Пе	Leu	Ser	
Tyr 65	His	Pro	Pro	Пе	Phe 70	Arg	Pro	Met	Lys	Arg 75	Ile	Thr	Trp	Asn	Thr 80	
Trp	Lys	Glu	Arg	Leu 85	Val	Ile	Arg	Ala	Leu 90		Asn	Arg	Val	G1y 95		
Tyr	Ser	Pro	His 100		Ala	Tyr	Asp	Ala 105		Pro	Gln	Gly	Val 110		Asn	
Trp	Leu	Ala 1 <b>1</b> 5	Lys	Gly	Leu	Gly	Ala 120		Thr	Ser	Arg	Pro 125		His	Pro	
Ser	Lys 130		Pro	Asn	Tyr	Pro 135		Glu	Gly	Asn	His 140		Val	Glu	Phe	
Asn 145		Asn	Tyr	Thr	G1n 150		Leu	Asp	Lys	Val 155		Ser	Ala	Val	Lys 160	
	Ile	Asp	Gly	Val 165		Val	Thr	Ser	Phe 170		Ala	Arg	Thr	Gly 175		

Glu	Glu	Gln	Thr 180	Arg	Пе	Asn	Leu	Asn 185	Cys	Thr	Gln	Lys	Ala 190	Leu	Met	
Gln	Val	Val 195	Asp	Phe	Leu	Ser	Arg 200	Asn	Lys	Gln	Leu	Tyr 205	Gln	Lys	Thr	
Glu	Ile 210	Leu	Ser	Leu	Glu	Lys 215	Pro	Leu	Leu	Leu	His 220	Thr	Gly	Met	Gly	
Arg 225	Leu	Cys	Thr	Leu	Asp 230	Glu	Ser	Val	Ser	Leu 235	Ala	Thr	Met	Ile	Asp 240	
Arg	Ile	Lys	Arg	His 245	Leu	Lys	Leu	Ser	His 250	Ile	Arg	Leu	Ala	Leu 255	Gly	
Val	Gly	Arg	Thr 260	Leu	Glu	Ser	Gln	Val 265	Lys	Val	Val	Ala	Leu 270	Cys	Ala	
		275				Leu	280					285			٠.	
	290				-	His 295		•			300					
305					310	Glu				315					320	
				325		Leu	•		330					11e 335	Asn	
Ile	He	Leu	Ser 340	Glu	Thr	Ąsp	Arg	Asp 345	Pro	Leu	Gln	Val	Va1 350			
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						ggt Gly										96
						ctg Leu										144

		atg Met												192
		aca Thr		_	-							-		240
_	-	aga Arg					_	-	-					288
	His	cct Pro 100	_										_	336
_		gct Ala		_	_			_						384
		tct Ser		_	-	-				_		-	-	432
		tgg Trp												480
		ctg Leu						-						528
		caa Gln 180			-			_			-	_	_	576
		ccg Pro	-	-		_				-				624
-		gat Asp			-								-	672

	Val	-	_			tca Ser		-		-		_	-				720
			-		-	gct Ala								-			768
						999 Gly											816
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Trp	Phe		Asn 20	Asn	Ala	Gly	Leu	Lys 25	Arg	Glu	Lys	Asp	G1n 30	Ser	Lys		
Gln	Val			Glu	Ser	Leu	Tyr 40		Ile	Ser	Cys	Tyr 45		Thr	Leu		
Val	G1u 50		Met	Met	Glu	Pro 55		Pro	Leu	Ser	Thr 60		Pro	Lys	Ile		
Ser 65		Asp	Thr	Pro	Leu 70	G1u	Met	Met	Thr	Ser 75		Arg	Ala	Ser	Trp 80		
	Leu	Val	Arg	Thr 85		Gln	Trp	Asn	G1u 90		Gln	Pro	Pro	Phe 95			

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Ala Asn His Pro Leu Leu Leu Ala Ala Asp Ala Val Gln Tyr Tyr Gln
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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
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Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
                        135
Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
                    150
                                        155
His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
                165
                                    170
Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Val Leu Gln
                                185
Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
                            200
Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
                        215
                                            220
Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Arg Gly
                    230
                                        235
Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
                245
                                    250
Thr Leu Leu Glu Val Cys Gly Ser Trp Pro Glu Gly Phe Gly Leu Arg
                                265
His Met Ser Ser Met Glu His Thr Glu Glu Gly Ser Gly Ser Asp Leu
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Pro Thr Pro Trp Pro Ser His Leu Ala Gly Thr Ser Trp Asp Pro Glu
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Gln Thr Gln Pro Leu Thr
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		-			-	aag Lys	-		-	-				_	_	144
						gac Asp 55	-				-		_			192
					-	aag Lys				_	_		-			240
			-		-	gct Ala	-		-	-		_			-	288
						gtc Val						Lys				336
				-		aaa Lys				-	_	-	_			384
Arg						cag Gln 135										432
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Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
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Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
                                     90
Ser Lys Ser Ser Ser Lys Val Thr Ser Val Pro Gly Lys Ala Ser Asp
            100
                                 105
Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
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                                     10
ctc ctc gca ggg ctt gca cta ctg gga gtc ggg ccg gtc cca gcg cgg
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Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
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		Asn		gcc Ala									144
				gac Asp 55						_	_		192
				aat Asn	-				-	-	_	-	240
				ccc Pro		-				-			288
				gta Val							-		336
				aca Thr									384
				ttc Phe 135									432
				aat Asn				-					480
-			 _	cta Leu			-						528
				ata Ile									576
				agt Ser		-	_					-	624

		195				200					205				
										tta Leu 220			aca Thr	67	72
L										ata Ile				72	20
				-	_			_	_	aaa Lys			_	76	58
										gat Asp				. 81	16
						-				aat Asn	-	_	~	86	54
										tgg Trp 300				91	.2
G										ttt Phe				96	50
										att Ile				100	8
										ctg Leu				105	6
			 -		_	-	-			ctg Leu		_		110	4
										atg Met				115	2

	370				375			380					
-	Glu	-	aca Thr	-			-	Ā٦a	_	-	~		1200
			att Ile										1248
			aca Thr 420		_								1296
			gat Asp										1344
			gac Asp										1392
			tat Tyr					Ala					1440
			tca Ser										1488
			tac Tyr 500										1536
			tac Tyr	-		•			_				1584
			gag Glu										1632
			cct Pro									-	1680

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	aaa Lys															1824
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1 Leu Ala Thr Phe 65 Asn	Ala Leu Leu Leu Leu Val	213> 400> Ala Ala His 35 Ala Leu	Homo 246 Ala Gly 20 Asn Ala Arg	Gly 5 Leu Val Phe Glu Phe 85	Arg Ala Thr Gly Arg 70 Lys	Leu Leu Ala Asp 55 Asn	Leu Glu 40 Leu Asp Lys	Gly 25 Leu Asn Leu Val	10 Val Phe Ser Ile Lys 90	Gly Gly Asp Val 75 Val	Pro Ala Lys 60 Phe Ser	Val Glu 45 Gln Leu Phe	Pro 30 Ala Thr Ala Lys	15 Ala Trp Asp Asp Asn 95	Arg Gly Leu Gln 80 His	
1 Leu Ala Thr Phe 65 Asn	Ala Leu Leu Leu 50 Val	213> 400> Ala Ala His 35 Ala Leu Pro Leu Asp	Homo 246 Ala Gly 20 Asn Ala Arg Tyr Ile 100	Gly 5 Leu Val Phe Glu Phe 85 Thr	Arg Ala Thr Gly Arg 70 Lys Ser	Leu Leu Ala Asp 55 Asn Pro Val	Leu Glu 40 Leu Asp Lys Val	Gly 25 Leu Asn Leu Val Pro 105	10 Val Phe Ser Ile Lys 90 Gly	Gly Gly Asp Val 75 Val Asp	Pro Ala Lys 60 Phe Ser	Val Glu 45 Gln Leu Phe Asp	Pro 30 Ala Thr Ala Lys Gly 110	15 Ala Trp Asp Asp Asn 95 Asp	Arg Gly Leu Gln 80 His	
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Phe	Phe	Asp	Ile	Tyr 405	Glu	Asp	Gly	Ile	Leu 410	Asp	Ile	Val	Val	Leu 415	Ser
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he	G1u	Ala 435	Asp	Ala	Tyr		Val 440	Lys	Val	Ile	Val	Leu 445		Gly	Leu
	Ser 450	Asn	Asp	Cys	Pro	Arg 455	Lys	Ile	Thr	Pro	Phe 460		Val	Asn	G1n
Pro 165	Gly	Pro	Tyr		Met 470	Tyr	Thr	Thr		Asp 475		Asn	Gly	Tyr	Leu 480
	Asn	Gly		A1 a 485	Gly	Gln	Leu				Ala	His	Leu	Ala 495	
iln	Leu	Pro	Tyr	Asn	Val	Leu	Gly			Arg	Ser	Ala	Asn		Leu

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Asp	His	Leu 515		Val	Gly	Ile	Pro 520		Pro	Ser	Gly	G1u 525			Ile	
Arg	Lys 530	Gln	Glu	Trp	Thr	A1 a 535		Ile	Pro	Asn	Ser 540	Gln	Leu	Ile	Val	
Ile 545	Pro	Tyr	Pro	His	Asn 550		Pro	Arg	Ser	Trp 555		Ala	Lys	Leu	Tyr 560	
Leu	Thr	Pro	Ser	Asn 565		Val	Leu	Leu	Thr 570	Ala	Ile	Ala	Leu	Ile 575	Gly	
Val	Cys	Val	Phe 580	Ile	Leu	Ala	Ile	Ile 585		Ile	Leu	His	Trp 590	Gln	Glu	
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	aga Arg															240

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	a gca e Ala							Asp								384
	a cga s Arg 130														-	432
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Thr	Leu	Cys 35	Gly	Gly	Leu	Tyr	Phe 40	Phe	Glu	Phe	Val	Ser 45	Cys	Ser	Ala	
Phe	Leu 50		Ser	Leu	Leu	Ile 55		Ile	Val	Tyr	Cys 60		Pro	Phe	Tyr	
Glu 65	Arg	Val	Asp	Thr	Thr 70		Val	Lys	Ser	Ser 75		Phe	Tyr	Ile	Thr 80	
	Gly	Thr	Gly	Cys 85		Phe	Leu	L.eu	Ala 90		He	Пe	Phe	Va1 95		
Thr	His	Asp	Arg 100		Ser	Ala		Ile 105		Ala	Пe	۷a٦	Phe 110		Phe	
Ile	Ala	Ser		Met	Phe	Leu			Phe	Ile	Thr	Met		Tyr	Glu	

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Lys	Arg 130			Ser	Gln	Leu 135			Pro	Glu	Asn 140		Thr	Arg	Ala	
Glu 145	Ala	Leu	Thr	Glu	Pro 150	Leu	Asn	Ala								٠
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								ctg Leu 140					432
								aag Lys					480
								gcc Ala					528
								gtg Val					576
								cta Leu					624
								gcc Ala 220	-		_		672
								cat His					720
						Пe		tcc Ser					768
	Asn				Val			gtg Val	His			i	816

	-	•	ggc Gly								_	-		-		864
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1			Thr	5					10			_	·	15		
Glu	He	Pro	Ala 20	Leu	Lys	Val	Val	Lys 25	Lys	Val	Lys	Ser	Met 30	Gln	Met	
Phe	His	Met 35	Pro	Ile	Thr		Ala 40	Met	Gln	Gly	Asp	Arg 45	Leu	Gly	Ile	
Cys	Val 50		Gln	Phe				Leu	Leu	G1u	Arg 60		Leu	Val	Cys	

Ala 65	Pro	Glu	Ser	Leu	His 70	Thr	Val	His	Ala	A1 a 75	Leu	Пe	Ser	Val	G1u 80
Lys	Ile	Pro	Tyr	Phe 85	Arg	Gly	Pro	Leu	G1n 90	Thr	Lys	Ala	Lys	Phe 95	
Ile	Thr	Val	Gly 100	His	Glu	Thr	Val	Met 105	Gly	Arg	Leu	Met	Phe 110	Phe	Ser
Pro	Ala	Pro 115	Asp	Asn	Phe	Asp	Gln 120	Glu	Pro	Ile	Leu	Asp 125	Ser	Phe	Asn
	130		Glu			135					140			•	
Thr 145	Pro	Ala	Val	Thr	Asp 150	Asn	Asp	Glu	Ala	Asp 155	Lys	Lys	Ala	Gly	Gln 160
			Gly	165					170	·				175	
			Val 180					185					190		_
		195	Asp				200		_			205			J
	210		His			215					220				
225			Lys		230			_		235		_			240
			Asp	245					250					255	_
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			tat Tyr 180						Leu			tag *				567
	<	211> 212>	252 188 PRT Homo	o saj	oien	s S										
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Leu	Arg	Ser	Leu 20	Asn	Ile	Leu	Ala	Ser 25	Ser	Thr	Tyr	Arg	Asn 30		Val	
Lys	Asn	A1a 35	Ser	Leu	Пe	Ser	Ala 40	Leu	Ser	Thr	Gly	Arg 45	Phe	Ser	His	
Ile	G]n 50		Pro	Val	Val	Ser 55		Thr	Pro	Arg	Leu 60	Thr	Thr	Ser	G1u	
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	Val	Leu	Pro	Ser 85	Val	Leu	Lys	Leu	Pro 90		Arg	Ser	Leu	Thr 95		
Phe	Ser	Ala	Arg 100		Gly	Lys	Arg	Lys 105		۷a٦	Lys	Ala	Val 110	Ile	Asp	
Arg	Phe	Leu 115		Leu	His	Cys	Gly 120		Trp	Val	Arg	Arg 125		Ala	Gly	
Tyr	Lys 130		Lys	Leu	Trp	Lys 135		Thr	Pro	Ala	Arg 140	Lys	Lys	Arg	Leu	
Arg 145		Phe	Val	Phe	Cys 150		Lys	Thr	Gln	Ser 155		Leu	Leu	Asp	Lys 160	
	Thr	Thr	Ser	Phe 165		Lys	Arg	Arg	Asn 170		Tyr	Val	Asp			
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											aag Lys 60					1	.92
cgc Arg 65	gaa Glu	aag Lys	aag Lys	caa G1n	cgt Arg 70	cag Gln	cgg Arg	gaa Glu	cag Gln	cag Gln 75	agg Arg	gat Asp	gtg Val	aac Asn	aac Asn 80	2	40
											gat Asp					2	88
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48

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Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Glu Leu Lys
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Arg Glu Lys Lys Gln Arg Gln Arg Glu Gln Gln Arg Asp Val Asn Asn
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Glu Pro Glu Pro Glu Glu Ala Glu Asp Tyr Ser Asp Gly Gln Ser Glu
                                    90
Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
                                105
Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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		_	agc Ser	~	_	 _			_					14	14
			att Ile											19	)2
	-	-	gga Gly							_		•		24	<b>0</b> 4
			gct Ala	-	-	-		_		-				28	18
-	_		gcc Ala 100						-					33	6
			gtt Val											38	4
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•	aca Thr							•						48	9

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-				aac Asn		_		_		-	_	-	_	_	192
				cca Pro 70											240
				ttt Phe								-			288
			_	ttt Phe			_	_	_	-					336
	-	-	•	ttc Phe	•			-	-		_				384
	_			ctc Leu							-		~		432
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His	Cys	Thr 35	Val	Pro	Ala	⊺yr	Asn 40	Phe	Pro	Val	Thr	Ala 45	Met	Ala	Ile	
Ala	Pro 50	Asn	Thr	Asn	Asn	Leu 55	Val	Ile	Ala	His	Ser 60	Asp	G1n	Gln	Val	
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	Gln	Lys	Gln	Gly 85		His	His	Leu	Trp 90	. •	G1n	Arg	Asp	Thr 95		
He	Thr	His	Ile 100		Phe	His	Pro	Lys 105	Arg	Pro	Met	His	Ile 110		Leu	
His	Asp	Ala 115	Tyr	Met	Phe	Cys	Ile 120	Ile	Asp	Lys	Ser	Leu 125		Leu	Pro	
Asn	Asp 130	Lys	Thr	Leu	Leu	Tyr 135	Asn	Pro	Phe	Pro	Pro 140	Thr	Asn	Asp	Пe	
11e 145	Ala	Gln	Leu	Pro	Pro 150	Pro	Ile	Lys	Lys	Lys 155	Lys	Phe	Gly	Thr		
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	ggc Gly											-	_		~	96
	ctt Leu															144
	ggc Gly 50															192
cag	cat	ctg	aga	gaa	agg	gat	tcc	aaa	cta	tac	ctc	cat	gag	ctc	cta	240

G1n 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80		
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						acc Thr										·	384
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taa																	627

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Glu	Leu	G1u 35	Ala	Ala	Leu	Gly	Lys 40	Lys	His	Lys	Gly	G1y 45	Asp	Ser	Ser	
Ser	Gly 50	Pro	Gln	Arg	Leu	Val 55	Ser	Phe	Arg	Leu	Ile 60	Arg	Asp	Leu	His	
G]n 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
G1u	Gly	Ser	Glu	Ile 85	Tyr	Leu	Pro	Glu	Va1 90	Val	Lys	Pro	Pro	Arg 95	Asn	
Pro	Glu	Leu	Val 100	Ala	Arg	Leu	Glu	Lys 105	Ile	Lys	Пe	Gln	Leu 110	Ala	Asn	
Glu	Glu	Tyr 115	Lys	Arg	Ile	Thr	Arg 120	Asn	Val	Thr	Cys	Gln 125	Asp	Thr	Arg	
His	Gly 130	Gly	Thr	Leu	Ser	Asp 135	Leu	Gly	Lys	Gln	Val 140	Arg	Ser	Leu	Lys	
Ala 145	Leu	Val	Ile	Thr	Ile 150	Phe	Asn	Phe	Ile	Val 155	Thr	Val	Val	Ala	Ala 160	
Phe	Val	Cys	Thr	Tyr 165	Leu	Gly	Ser	Gln	Tyr 170	Ile	Phe	Thr	Glu	Met 175	Ala	
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		۷al			cat His							Asp				1	192
	Gly				aca Thr 70						Thr					2	240
					gtg Val											2	:88
gag Glu	gtg Val	gac Asp	atg Met 100	gct Ala	cac His	aga Arg	ttt Phe	gct Ala 105	cag Gln	gag Glu	tac Tyr	aag Lys	aaa Lys 110	gac Asp	cct Pro		36
					gct Ala											3	84
					gat Asp											4	32
					ggc Gly 150											4	80
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tcg Ser	gcc Ala	cag G1n	ctg Leu 180	aca Thr	cac His	gcc Ala	Ser	tcc Ser 185	ctg Leu	ggt Gly	tac Tyr	aat Asn	ggc Gly 190	gcc Ala	atc Ile	57	76
ctg	cag	gcc	ctg	gct	gtg	cac	ctg	gcc	ttg	cag	ggc	gag	tct	tcc	agc	62	24

Lei	ı G1r	195	a Leu 5	ı Alā	a Val	His	Leu 200		l Lei	G]r	ı Gly	G1u 205		Ser	Ser	
gaç Glu	) cad   His   210	Phe	ctc Leu	aag Lys	caa Gln	ctc Leu 215	Leu	ggc Gly	cac His	atg Met	gag Glu 220	Asp	ctg Leu	gag Glu	ggt Gly	672
gat Asp 225	A la	caç Glr	tcc Ser	gtc Val	ttg Leu 230	Asp	gcc Ala	agg Arg	gag Glu	ttg Leu 235	ggc Gly	atg Met	gag Glu	gag Glu	cgt Arg 240	720
cca Pro	tac Tyr	tcc Ser	: agc :Ser	cgc Arg 245	Leu	aag Lys	aag Lys	att Ile	gga Gly 250	gag Glu	ctt Leu	cta Leu	gac Asp	cag G1n 255	Ala	768
tcg Ser	gtg Val	acc Thr	agg Arg 260	Glu	gaa Glu	gtg Val	gtg Val	tct Ser 265	gag Glu	cta Leu	999 Gly	aat Asn	ggc Gly 270	att Ile	gct Ala	816
			Ser								ttc Phe					864
											agc Ser 300					912
ctc Leu 305	att Ile	tat Tyr	tcc Ser	atc Ile	tca Ser 310	ctt Leu	ggt Gly	999 Gly	gac Asp	aca Thr 315	gac Asp	acc Thr	att Ile	gcc Ala	acc Thr 320	960
atg Met	gct Ala	999 Gly	gcc Ala	att Ile 325	gct Ala	ggt Gly	gcc Ala	tac Tyr	tat Tyr 330	ggg Gly	atg Met	gat Asp	G1n	gtg Val 335	cca Pro	1008
gag Glu	agc Ser	tgg Trp	cag Gln 340	caa Gln	agc Ser	tgt Cys	gaa Glu	ggc Gly 345	tac Tyr	gag Glu	gag Glu	Thr	gac Asp 350	atc Ile	ctg Leu	1056
	Gln				cgt Arg	Val					tga *					1092

<210> 262 <211> 363 <212> PRT <213> Homo sapiens

<400> 262

Met Ala Ala Ala Ala Ala Ala Ala Gly Gly Ala Gly Ala Ala Arg Ser Leu Ser Arg Phe Arg Gly Cys Leu Ala Gly Ala Leu Leu 25 Gly Asp Cys Val Gly Ser Phe Tyr Glu Ala His Asp Thr Val Asp Leu Thr Ser Val Leu Arg His Val Gln Ser Leu Glu Pro Asp Pro Gly Thr Pro Gly Ser Glu Arg Thr Glu Ala Leu Tyr Tyr Thr Asp Asp Thr Ala 70 75 Met Ala Arg Ala Leu Val Gln Ser Leu Leu Ala Lys Glu Ala Phe Asp Glu Val Asp Met Ala His Arg Phe Ala Gln Glu Tyr Lys Lys Asp Pro 105 Asp Arg Gly Tyr Gly Ala Gly Val Val Thr Val Phe Lys Lys Leu Leu 115 Asn Pro Lys Cys Arg Asp Val Phe Glu Pro Ala Arg Ala Gln Phe Asn 135 140 Gly Lys Gly Ser Tyr Gly Asn Gly Gly Ala Met Arg Val Ala Gly Ile 150 155 Ser Leu Ala Tyr Ser Ser Val Gln Asp Val Gln Lys Phe Ala Arg Leu Ser Ala Gln Leu Thr His Ala Ser Ser Leu Gly Tyr Asn Gly Ala Ile 185 Leu Gln Ala Leu Ala Val His Leu Ala Leu Gln Gly Glu Ser Ser Ser 195 200 Glu His Phe Leu Lys Gln Leu Leu Gly His Met Glu Asp Leu Glu Gly 215 220 Asp Ala Gln Ser Val Leu Asp Ala Arg Glu Leu Gly Met Glu Glu Arg 230 235 Pro Tyr Ser Ser Arg Leu Lys Lys Ile Gly Glu Leu Leu Asp Gln Ala 250 Ser Val Thr Arg Glu Glu Val Val Ser Glu Leu Gly Asn Gly Ile Ala 260 265 Ala Phe Glu Ser Val Pro Thr Ala Ile Tyr Cys Phe Leu Arg Cys Met 280 Glu Pro Asp Pro Glu Ile Pro Ser Ala Phe Asn Ser Leu Gln Arg Thr 295 300

	Let 305	u II:	е Ту	r Se	r Ile	Sei 310		u Gly	/ G1y	/ Asp	7hr 315		o Thi	^ I1e	e Ala	a Thr 320	
			a G1	y A1	a Ile 329	e Ala		/ A1a	a Tyr	Tyr 330	· Gly		t Asp	Glr	n Va ⁻ 335	l Pro	
	GΊι	ı Sei	r Tr	p G1i 340	n G1r		Cys	s Glu	Gly 345	/ Tyr		ı G1ı	ı Thr	. Ast	o Ile	e Leu	
	Αla	a Gla	1 Sei 35!		ı His	Arg	y Val	260	e Glr		Ser	•			,		
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	acc Thr	cat His	gag Glu	ctg Leu 20	ctg Leu	ctg Leu	agc Ser	tgt Cys	gta Val 25	ttc Phe	cgg Arg	ctg Leu	gag Glu	ttc Phe 30	ctc Leu	ccg Pro	96
(	gaa Glu	aga Arg	aca Thr 35	tca Ser	999 Gly	ggt Gly	cca Pro	gag Glu 40	gca Ala	gcc Ala	gac Asp	ttc Phe	tct Ser 45	gac Asp	cag G1n	ctg Leu	144
5	tcg Ser	tta Leu 50	gga Gly	agc Ser	agc Ser	agg Arg	gtc Val 55	cct Pro	cgg Arg	tgt Cys	ggg Gly	caa Gln 60	999 Gly	act Thr	ctg Leu	ctg Leu	192
P	oct Ala 65	cag Gln	gcc Ala	tgc Cys	Gln	gac Asp 70	ctc Leu	ccc Pro	agc Ser	atc Ile	cgc Arg 75	aac Asn	tgc Cys	tac Tyr	ctg Leu	act Thr 80	240
H	at lis	tgc Cys	tcg Ser	cca Pro	gcc Ala 85	cga Arg	gcc Ala	agt Ser	ctg Leu	ctg Leu 90	gcc Ala	tcc Ser	cag G1n	gct Ala	ctg Leu 95	cac His	288
С	ga	999	gag	cta	cag	cga	gtc	сса	acc	ctg	cta	ctg	ссс	atg	cct	acg	336

Arg	Gly	Glu	Leu 100		Arg	Va1	Pro	Thr 105		Leu	ı Leu	Pro	Met 110		Thr	
			Leu					Pro			cca Pro					384
tac Tyr	cac His 130	cgg Arg	gct Ala	tca Ser	gac Asp	acc Thr 135	Pro	tcg Ser	gga Gly	ctc Leu	tct Ser 140	ccc Pro	aca Thr	gac Asp	acc Thr	432
atg Met 145	ggc Gly	aca Thr	gcc Ala	atg Met	cgg Arg 150	gtc Val	ctg Leu	cag Gln	tgg Trp	gtg Val 155	cta Leu	gtt Val	ttg Leu	gag Glu	agc Ser 160	480
tgg Trp	cgc Arg	ccc Pro	cag Gln	gct Ala 165	ctc Leu	tgg Trp	gct Ala	gtg Val	ccc Pro 170	cct Pro	gct Ala	gcc Ala	`cgc Arg	ctg Leu 175	gca Ala	528
											ctg Leu					576
											cag Gln					624
											ctc Leu 220					672
											cat His					720
tct Ser	ttt Phe	999 Gly	Asp	cac His 245	ctc Leu	ttt Phe	999 Gly	Ala	ctg Leu 250	gtc Val	ctc Leu	ctg Leu	ccc. Pro	ctg Leu 255	cag Gln	768
		Phe					Arg				ttt Phe	Gly				816
ga i	gcc	ttg	cga	gct	ctg	agc	ctg	cct	ctg	acc	cag	ttg	cct	gtg	tcc	864

Gly	Ala	Leu 275	_	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	•
	gag Glu 290										_	-				912
	tac Tyr															960
	gtg Val			-								_				1008
	cag Gln															1056
	ctg Leu															1104
	ctg Leu 370															1152
	tat Tyr															1200
	tca Ser		Val					Val				tag *				1239
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<212> PRT

<213> Homo sapiens

<400> 264

Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser Glu Tyr Leu  $1 \ 5 \ 10 \ 15$ 

Thr	His	G1ı	ı Let 20	ı Let	ı Leu	s Ser	Cys	Va 25	Phe	e Arç	g Lei	u G1u	u Phe 30	e Leu	ı Pro
Glí	ı Arg	35 Thr	` Ser	· Gly	/ Gly	Pro	G1u 40	ı Alá	a Ala	a Asp	) Phe	e Ser 45	· Asp	G]r	ı Let
Ser	Leu 50	ı Gly	/ Ser	` Ser	` Arg	Va1 55	Pro	Arg	J Cys	Gly	/ G1r 60	n Gly	/ Thr	. Ler	. Lei
65					Asp 70					75					80
				85	Arg				90					95	
			100	1	Arg			105	,				110		
		115	1		Thr		120					125			
	130				Asp	135					140	l		•	
145					Arg 150					155					160
				165					170				_	175	
			180		Phe			185					190		
		195			Val		200					205			
	210				Leu	215					220				
225					Tyr 230					235					240
				245	Leu				250					255	
			260		Thr			265					270		
		275			Leu		280					285			
	290					295					300				
305					Leu 310					315					320
				325	Val				330					335	
			340		Ser -			345					350	_	
1et	Leu	G]n	Lys	Thr	Trp		Leu 360	Ala	Asp	G1u	Gly	Leu	Arg	Gln	His

Leu	Leu 370		s Tyr	^ Lys	: Lei	2 Pro 375		) Ser	- Thr	Let	2 Pro 380		u Gly	y Phe	e Glu	
Leu 385	Tyr		^ G]r	1 Leu	2 Pro	Pro		ı Arg	g G1r	His 395	Tyr		u G1r	n Arg	Leu 400	
Thr	Ser	Thr	^ Val	405	ı Glr		Gly	√ VaT	Ser 410	· Glu		,			100	
	<	211> 212>	> 265 > 576 > DNA > Hom	5	pien	S										
	<		CDS	(	576)											
			265													•
atg Met 1	gcg Ala	ggc Gly	gct Ala	gca Ala 5	gaa Glu	gat Asp	gcg Ala	cga Arg	gct Ala 10	ctt Leu	ttc Phe	cgg Arg	gct Ala	999 Gly 15		48
tgc Cys	gcg Ala	gcc Ala	ctg Leu 20	gag Glu	gcc Ala	tgg Trp	ccg Pro	gcc Ala 25	ttg Leu	cag Gln	atc Ile	gct Ala	gtg Val 30	gag Glu	aat Asn	96
ggc Gly	ttc Phe	ggg Gly 35	ggt Gly	gtg Val	cac His	agc Ser	cag Gln 40	gag Glu	aag Lys	gcc Ala	aag Lys	tgg Trp 45	Leu	999 Gly	ggt Gly	144
gca Ala	gtg Val 50	gag Glu	gat Asp	tac Tyr	ttc Phe	atg Met 55	cgc Arg	aat Asn	gct Ala	gac Asp	ttg Leu 60	gag Glu	cta Leu	gat Asp	gag Glu	192
gtg /a1 65	gaa Glu	gac Asp	ttc Phe	ctt Leu	gga Gly 70	gag Glu	ctg Leu	ttg Leu	acc Thr	aac Asn 75	gag Glu	ttt Phe	gat Asp	aca Thr	gtt Val 80	240
jtg /al	gaa Glu	gac Asp	999 Gly	agt Ser 85	ctg Leu	ccc Pro	cag Gln	gtg Val	agc Ser 90	cag Gln	caa Gln	ctg Leu	cag Gln	acc Thr 95	atg Met	288
tc ( he l	cac His	cac His	ttc Phe 100	cag Gln	agg Arg	ggt Gly	Asp	ggg Gly 105	gct Ala	gct Ala	ctg Leu	agg Arg	gag Glu 110	atg Met	gcc Ala	336

tcc Ser	tgo Cys	ato Ile 115	Thr	cag Glr	aga Arg	aaa Lys	tgc Cys 120	Lys	gto Val	aca Thr	a gcd Ala	act Thr	' Ala	ctt Leu	aag Lys	384
aca Thr	gct Ala 130	Arg	gag Glu	act Thr	gat Asp	gag Glu 135	Asp	gaa Glu	gat Asp	gat Asp	gtg Val 140	Asp	agt Ser	gtg Val	gaa Glu	432
gag Glu 145	Met	gag Glu	gtc	aca Thr	gct Ala 150	acg Thr	aat Asn	gat Asp	999 Gly	gct Ala 155	gct Ala	aca Thr	gat Asp	999 Gly	gtc Val 160	480
tgc Cys	ccc Pro	cag Gln	cct Pro	gaa Glu 165	ccc Pro	tct Ser	gat Asp	cca Pro	gac Asp 170	gct Ala	cag Gln	act Thr	att Ile	aag Lys 175	gaa Glu	528
gag Glu	gat Asp	ata Ile	gtg Val 180	gaa Glu	gat Asp	ggc Gly	tgg Trp	acc Thr 185	att Ile	gtc Val	cgg Arg	aga Arg	aaa Lys 190	aaa Lys	tga *	576
	<2 <2	210> 211> 212> 213>	191 PRT	o sap	oiens	5										
Met 1		100> Gly		Ala 5	G1u	Asp	Ala	Arg	Ala 10	Leu	Phe	Arg	Ala	Gју 15	Val	
Cys	Ala	Ala	Leu 20		Ala	Trp	Pro	A1a 25		Gln	Ile	Ala			Asn	
Gly	Phe	Gly 35		Val	His	Ser	G1n 40		Lys	Ala	Lys		30 Leu	Gly	Gly	
Ala	Val 50		Asp	Tyr	Phe	Met 55	Arg		Ala			45 G1u	Leu	Asp	Glu	
Val (		Asp	Phe		Gly 70							Phe	Asp			
Val	G1u	Asp				Pro	Gln				Gln	Leu		Thr	80 Met	
Phe I	His	His			Arg	Gly		Gly	90 Ala	Ala	Leu		Glu	95 Met	Ala	
Ser (	Cys			Gln	Arg			105 Lys	Val	Thr			110 Ala	Leu	Lys	

Thi	^ Ala		g Glu	u Thr	· Asp	Glu 135		o Glu	ı Asp	) Ası	> Va ⁻ 14(		Sei	r Val	l Glu	
G1u 145	ı Met		ı Va	l Thr	` Ala 150	Thr		n Asp	GTy	/ Ala 159	a Ala		^ Asp	o Gly	/ Val 160	
Cys	Pro	G]r	n Pro	Glu 165		Ser	· Asp	) Pro	Asp 170	Ala		Thi	· Ile	Lys 175	G1u	
Glu	ı Asp	) Il€	2 Val 180	Glu )	ı Asp	Gly	Trp	7hr 185		e Val	l Arg	J Arç	) Lys 190	_	5	
	<	:211> :212>	<ul><li>267</li><li>567</li><li>DNA</li><li>Horr</li></ul>	•	pien	S										
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gcg Ala	tgc Cys	gtc Val	gcg Ala 20	gcc Ala	cac His	ggc Gly	ttc Phe	cgt Arg 25	atc Ile	cat His	gat Asp	tat Tyr	ttg Leu 30	tac Tyr	ttt Phe	96
			Ser	cct Pro												144
gcc Ala	aag Lys 50	gac Asp	ttt Phe	ggt Gly	ggt Gly	atc Ile 55	ttt Phe	cac His	aca Thr	agg Arg	tat Tyr 60	gag Glu	cag Gln	att Ile	cac His	192
ctt Leu 65	gtc Val	ccc Pro	gct Ala	gaa Glu	cct Pro 70	cca Pro	gag Glu	gcc Ala	tgc Cys	999 Gly 75	gaa Glu	ctc Leu	agc Ser	aac Asn	ggt Gly 80	240
ttc Phe	ttc Phe	atc Ile	cag G1n	gac Asp 85	cag G1n	att Ile	gct Ala	ctg Leu	gtg Val 90	gag Glu	agg Arg	999 Gly	ggc Gly	tgc Cys 95	tcc Ser	288
ttc	ctc	tcc	aag	act	cgg	gtg	gtc	cag	gag	cac	ggc	ggg	caa	aca	at.a	336

Phe	e Lei	ı Sei	r Lys 10(		· Arg	ı Val	Val	G]r 105		ı His	Gly	/ Gly	/ Arg 11(		a Val	
ato Ile	ato Ile	tct Ser	· Asp	aac Asn	gca Ala	gtt Val	gac Asp 120	) Asr	gac Asp	ago Ser	tto Phe	tad Tyr 125	` Val	gaq Glu	atg ıMet	384
ato	cag e Gln 130	Asp	agt Ser	acc Thr	cag G1n	cgc Arg 135	Thr	gct Ala	gac Asp	atc Ile	e ccc Pro	Ala	cto Leu	tto Phe	ctg Leu	432
	ı Gly										Leu				999 Gly 160	480
ctg Leu	cca Pro	tgg Trp	gcc Ala	atc Ile 165	att Ile	tcc Ser	atc Ile	cca Pro	gtc Val 170	Asn	gtc Val	acc Thr	agc Ser	ato Ile 175	ccc	528
acc Thr	ttt Phe	gag Glu	ctg Leu 180	ctg Leu	caa Gln	ccg Pro	ccc Pro	tgg Trp 185	acc Thr	ttc Phe	tgg Trp	tag *				567
	· </td <td>211&gt; 212&gt;</td> <td>268 188 PRT Homo</td> <td>o sap</td> <td>oiens</td> <td>5</td> <td></td>	211> 212>	268 188 PRT Homo	o sap	oiens	5										
	</td <td>100&gt;</td> <td>268</td> <td></td>	100>	268													
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41a	Cys	Val	Ala 20	Ala	His	Gly	Phe	Arg 25	Пe	His	Asp	Tyr	Leu 30	Tyr	Phe	
Gln	Val	Leu 35	Ser	Pro	G1y	Asp	Ile 40		Tyr	Ile	Phe	Thr 45		Thr	Pro	
Ala	Lys 50		Phe	Gly		Ile 55		His	Thr	Arg	Tyr 60		Gln	Ile	His	
_eu 55	Val	Pro	Ala				Glu	Ala	Cys	Gly 75		Leu	Ser	Asn	Gly 80	
he	Phe	Пe	Gln			Ile	Ala	Leu	Val 90		Arg	Gly	Gly	Cys 95	Ser	
he	Leu	Ser			Arg	Val		Gln 105		His	Gly	Gly	Arg 110		Val	

Πe	: I1e	Ser 115		Asr	ı Ala	a Val	Asp 120		ı Asp	Ser	Phe	Tyr 125		Glu	ı Met	
He	Glr 130	Asp		Thr	Glr	135	Thr		ı Asp	Ile	Pro 140	Ala		ı Phe	e Leu	
Leu 145		' Arg	Asp	Gly	Tyr 150		Ile	· Arg	ı Arg	Ser 155		ı Glu	G]r	n His	Gly 160	
				165					170	_			Ser	175 175	Pro	
Thr	Phe	Glu	Leu 180		Gln	Pro	Pro	Trp 185		Phe	Trp	)				
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	<	220> 221> 222>			1419	)										
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		Leu													Thr	
		ctc Leu														96
		agg Arg 35														144
ggc Gly	cac His 50	gtc Val	ttg Leu	agc Ser	ctg Leu	ggc Gly 55	gcc Ala	agc Ser	agc Ser	ttc Phe	gtg Val 60	gag Glu	gag Glu	gag G1u	cac His	192
		tgg Trp														240
		tac Tyr														288

										aca Thr					336
										aaa Lys					384
		Thr								aag Lys 140					432
_	Ser	_				_				ctg Leu					480
										gac Asp					528
		_		-						gtc Val			-		576
			-	_			-	_		999 Gly					624
					-					gtc Val 220					672
	-			_	-					ccg Pro	_	_		_	720
										tat Tyr					768
										aaa Lys			-		816

					tta Leu			864
					aga Arg			912
					cta Leu 315			960
					att Ile			1008
					ggc Gly			1056
					ggc Gly			1104
					999 Gly			1152
					ctg Leu 395			1200
					tgc Cys			1248
					gtg Val			1296
					aaa Lys			1344

atg cac ctg ctc att aca gct gct gtc tgt gta ttc ttc acg gca atg 1392 Met His Leu Leu Ile Thr Ala Ala Val Cys Val Phe Phe Thr Ala Met 460 450 455 1419 gat caa acc aga ctc aca cag tct tag Asp Gln Thr Arg Leu Thr Gln Ser * 465 470 <210> 270 <211> 472 <212> PRT <213> Homo sapiens <400> 270 Met Val Leu Ala Ser Ala Leu Leu Cys Val Ile Val Ser Val Leu Thr Asn Val Leu Val Gly Gly Asn Thr Pro Arg Lys Asn Pro Met His Pro 25 Ser Ser Arg Trp Ser Glu Leu Asp Leu Leu Ile Leu Leu Gly Thr Ala 40 Gly His Val Leu Ser Leu Gly Ala Ser Ser Phe Val Glu Glu His 55 Gln Thr Trp Tyr Phe Leu Val Asn Thr Leu Cys Leu Ala Leu Ser Gln 70 75 Glu Thr Tyr Arg Asn Tyr Phe Leu Gly Asp Asp Gly Glu Pro Pro Cys 90 Gly Leu Cys Val Glu Gln Gly His Asp Gly Ala Thr Ala Ala Trp Gln 105 Asp Gly Pro Gly Cys Asp Val Leu Glu Arg Asp Lys Gly His Gly Ser 120 125 Pro Ser Thr Ser Glu Val Leu Arg Gly Arg Glu Lys Trp Met Val Leu 140 135 Ala Ser Pro Trp Leu Ile Leu Ala Cys Cys Arg Leu Leu Arg Ser Leu 150 155 Asn Gln Thr Gly Val Gln Trp Ala His Arg Pro Asp Leu Gly His Trp 170 Leu Thr Ser Ser Asp His Lys Ala Glu Leu Ser Val Leu Ala Ala Leu 185 Ser Leu Leu Val Val Phe Val Leu Val Gln Arg Gly Cys Ser Pro Val 200 205 Ser Lys Ala Ala Leu Ala Leu Gly Leu Leu Gly Val Tyr Cys Tyr Arg 210 215 220

Ala	Ala	Ile	Gly	Ser	Val	Arg	Phe	Pro	Trp	Arg	Pro	Asp	Ser	Lys	Asp
225					230					235	_				240
			·	245					250		Tyr			255	
Gly	Ile	Leu	Phe 260	Thr	Gly	Thr	Lys	Asp 265	Leu	Leu	Lys	Ser	G1n 270	Val	He
Ala	Ala	Asp 275		Lys	Leu	Lys	Thr 280	Val	Gly	Leu	Trp	G1u 285	He	Tyr	Ser
Gly	Leu 290	Val	Leu	Leu	Ala	Ala 295	Leu	Leu	Phe	Arg	Pro 300	His	Asn	Leu	Pro
Va1 305	Leu	Ala	Phe	Ser	Leu 310	Leu	Пe	Gln	Thr	Leu 315	Met	Thr	Lys	Phe	Ile 320
		Pro	Leu	Arg 325		Asp	Alá	Ala	G1u 330	Ile	Thr	Val	Met	His 335	Tyr
Trp	Phe	Gly	G1n 340		Phe	Phe	Tyr	Phe 345		Gly	Asn	Ser	Asn 350		Ile
Ala	Thr	Va1 355		Ile	Ser	Ala	Gly 360		۷al	Gly	Leu	Asp 365		Tyr	Val
Glu	Ile 370		Ala	Val	Leu	Leu 375		Ala	Phe	Gly	Thr 380		Ala	Gly	Pro
Va1 385	Leu	Trp	Ala	Ser	His 390		Val	His	Phe	Leu 395	Ser	Ser	G1u	Thr	Arg 400
		Ser	Ala	Leu 405		His	Ala	Cys	Phe 410		Tyr	Ala	Leu	Ile 415	
Ser	Ile	Pro	Va1 420		Thr	Tyr	He	Val 425		Val	Thr	Ser	Leu 430		Tyr
His	Leu	Phe 435		Trp	Ser	Val	Phe 440		Pro	Lys	Leu	Leu 445		Glu	Gly
Met	His 450		Leu	Ile	Thr	Ala 455		Val	Cys	Val	Phe 460		Thr	Ala	Met
Asp 465	Gln	Thr	Arg	Leu	Thr 470		Ser								
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			1089	9											
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	<2	213>	Homo	s ap	oiens	S									
	<2	220>													
		221>	CDS					•							
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				(											

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															ctc Leu		96
	gtg Val	cag Gln	aac Asn 35	ctg Leu	ctg Leu	tcg Ser	ggc Gly	tgg Trp 40	ctg Leu	ggc Gly	agc Ser	gag Glu	gac Asp 45	gcc Ala	gcc Ala	ttc Phe	144
	gtg Val	ccc Pro 50	ttc Phe	cac His	ttg Leu	cgc Arg	cgc Arg 55	acg Thr	gcc Ala	gcc Ala	acg Thr	ctg Leu 60	ttg Leu	tgc Cys	cac His	tcg Ser	192
	ctg Leu 65	ctg Leu	ccg Pro	ctc Leu	ggc Gly	tac Tyr 70	tat Tyr	gtg Val	ggc Gly	atg Met	tgc Cys 75	ctt Leu	gcg Ala	gct Ala	tca Ser	gaa Glu 80	240
	aag Lys	cgg Arg	ctc Leu	cac His	gcc Ala 85	ctc Leu	agc Ser	cag Gln	gcc Ala	cct Pro 90	gag Glu	gcc Ala	tgg Trp	cgg Arg	ctc Leu 95	ttc Phe	288
	ctg Leu	ctg Leu	ctg Leu	gcc Ala 100	gtg Val	acc Thr	ctc Leu	ccc Pro	tcc Ser 105	atc Ile	gcc Ala	tgc Cys	atc Ile	ctg Leu 110	atc Ile	tac Tyr	336
															acc Thr		384
	gcc Ala	ctc Leu 130	tac Tyr	gcc Ala	ctc Leu	cca Pro	cag Gln 135	tct Ser	ggc Gly	tgg Trp	cag Gln	gct Ala 140	gtt Val	gcc Ala	tcc Ser	tct Ser	432
	gtc Val 145	aac Asn	act Thr	gag Glu	ttc Phe	cgg Arg 150	cgg Arg	att Ile	gac Asp	aag Lys	ttt Phe 155	gcc Ala	acc Thr	ggt Gly	gca Ala	cca Pro 160	480
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Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	Ala 265	Ser	Leu	Val	Glu	Val 270	Asn	Pro	
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taa *																•	723
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Cys Ala Xaa	gtg cgg agg ctg Val Arg Arg Leu 70	Val Leu Arg G	ly Leu Ala Asn L	eu Ala
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Thr	Thr	Cys	Lys	His 245	Leu	Met	His	His	Phe 250	Pro	Asp	Leu	Leu	Gly 255	Arg		
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	atc Ile					-	-	-	_	_	_				~ ~	;	336
	ctc Leu															;	384
	aaa Lys 130															4	432
	ggc Gly												-	-		2	480
	ctg Leu															Ę	528
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Asp Pro Arg Asp Val Lys Asn Met Asn Thr Trp Leu Leu Phe Leu Pro
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Leu Phe Pro Val Gln Val Gln Thr Leu Ile Val Val Ile Ile Gly Met
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Tyr Leu Ile Asn Asn Arg Lys Glu Glu Ser Ser Lys His Gln Ala Val
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Arg Lys Asp Pro Tyr Val Gln Met Asp Lys Gly Val Leu Gln Gln Gly
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-			Phe		-	ctt Leu			_							624
	-	-			-	aca Thr 215	_							_	_	672
						ttt Phe										720
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Asp	Val 50		Tyr	Arg	Leu	Pro 55	Phe	Thr	Пe	Asn	Asn 60	Leu	Thr	Ile	Asn	
I1e 65	Asn	Ile	Leu	Leu	Pro 70	Pro	Gln	Phe	Pro	G1n 75	Glu	Lys	Pro	Val	Ile 80	
Ser	Val	Tyr	Pro	Pro 85	Ile	Arg	His	His	Leu 90	Met	Asp	Lys	Gln	G1y 95	Val	
Tyr	Val	Thr	Ser 100	Pro	Leu	Val	Asn	Asn 105	Phe	Thr	Met	His	Ser 110	Asp	Leu	
Gly	Lys	Ile 115	Ile	Gln	Ser	Leu	Leu 120	Asp	Glu	Phe	Trp	Lys 125	Asn	Pro	Pro	
Val	Leu 130	Ala	Pro	Thr	Ser	Thr 135	Ala	Phe	Pro	Tyr	Leu 140	Tyr	Ser	Asn	Pro	
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Lys	Arg 370	Thr	Ile	Cys	His	Cys 375	Arg	Arg	Ala	Lys	G1u 380	Glu	Lys	Leu	Gln	
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Lys 145	Lys	Glu	Tyr	Glu	Asp 150	Ala	Glu	Asn	Thr	Ser 155	Thr	Gln	Ser	Lys	Val 160
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Lys	Thr	Glu 195	Glu	Val	Val	Leu	Lys 200	Asp	Gly	Arg	Ile	G1u 205	Arg	Leu	Lys
Leu	Glu 210	Leu	Glu	Arg	Lys	Asp 215	Ala	Glu	Ile	Gln	Lys 220	Leu	Lys	Asn	Val
Ile 225	Thr	Gln	Trp	Glu	A1 a 230	Lys	Tyr	Lys	Glu	Val 235	Lys	Ala	Arg	Asn	A1a 240
Gln	Leu	Leu	Lys	Met 245	Leu	Gln	Glu	Gly	G1u 250	Met	Lys	Asp	Lys	Ala 255	Glu
Пe	Leu	Leu	G1n 260	Val	Asp	Glu	Ser	G1n 265	Ser	Ile	Lys	Asn	G1u 270	Leu	Thr
Ile	Gln	Val 275	Thr	Ser	Leu	His	Ala 280	Ala	Leu	Glu	G1n	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	Glņ	Ala	G1u 295	Leu	Ala	Lys	Tyr	G1n 300	Gly	Gly	Arg	Lys
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WO 01/29221

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					-	_		agt Ser							-	288
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	-	-	_	_				ctt Leu								384
								tct Ser			_					432
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Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	Gln 160	
			-		aac Asn											528
					tcc Ser										-	576
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_	_		_	-	gac Asp 230		_				_	_			_	720
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					gag Glu											816
					gaa Glu				_	_	_					864
					ccc Pro											912
					att Ile 310											960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	сса	agg	gcc	agg	gat	ttc	1008

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	G1n	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe	
											aac Asn					1056
											acc Thr					1104
											gcc Ala 380					1152
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											agt Ser					1248
											tgt Cys					1296
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Trp	Ser	His 35	20 Arg	Arg	His	Val	Met 40	25 Gln	G1n	G1y	Glu	Gln 45	30 G1n	Gln	Ile	

Pro	Asp 50	Pro	Cys	Arg	Leu	Ser 55	Thr	Ala	Thr	Leu	Lys 60	Cys	Leu	G1n	Ala
G1n 65	Ala	Met	Arg	Glu	Gly 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asr 80
Leu	Trp	Thr	Leu	Leu 85	Ser	Ser	Pro	Ser	Thr 90	His	His	Ile	Gly	Va1 95	Cys
Ser	Leu	Ala	Arg 100	Ser	Met	Ala	Val	Trp 105	Gln	His	Gly	Val	Ile 110	Leu	Asp
Ile -	Met	Glu 115	Gln	Leu	Leu	Ser	Ser 120	Leu	Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr
Arg	Ile 130	Thr	Gly	Ala	Ala	Phe 135	Phe	Ser	Glu	Leu	Met 140	Lys	Glu	Pro	Пе
Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	Ile	Leu	Met	Asp	G1r 160
Ser	Ala	Trp	Asp	Ser 165	Asn	Ala	Thr	Leu	Arg 170	Gln	Met	Ala	Ile	Arg 175	Gly
Leu	Gly	Asn	Thr 180	Ala	Ser	Gly	Ala	Pro 185	His	Lys	Val	Lys	Lys 190	His	Lys
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Thr	Glu 210	Val	Val	Cys	Glu	Ser 215	Leu	Lys	Ala	Leu	Lys 220	Lys	Ile	Leu	Glu
Leu 225	Leu	Thr	Asp	Arg	Asp 230	Val	Ser	Phe	Tyr	Phe 235	Lys	Glu	Ile	Val	Let 240
Gln	Thr	Arg	Thr	Phe 245	Phe	Glu	Asp	Glu	G1n 250	Asp	Asp	Val	Arg	Leu 255	Thr
Ala	Ile	Phe	Leu 260	Phe	Glu	Asp	Leu	Ala 265	Pro	Leu	Thr	Gly	Arg 270	Arg	Trp
Lys	Ile	Phe 275	Phe	Ala	Glu	Glu	Ile 280	Lys	Lys	Ser	Leu	I1e 285	Ser	Phe	Leu
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Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln		Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	A1a 345	Lys	Lys	Asn	Gln	G1u 350	Ile	Leu
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Arg	Leu	Gln	Ala	Leu 405	Arg	Gln	Asp	Pro	Cys 410	Ile	Ser	Val	Gln	Arg 415	Ala		
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					aag Lys			-								30	36

	gcc Ala		-	-	-					-			_		384
	aca Thr 130													_	432
	tgg Trp													-	480
	ctc Leu	-										-	-	_	528
	agt Ser														576
	gca Ala		-				-					-		-	624
	tat Tyr 210			_	_	_		-							672
	ttt Phe														720
	ctg Leu		Lys	Ser	Leu		Asp		Glu					Tyr	768
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Phe	Lys 130	G1n	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	Gln,	Cys 140	Gly	Leu	Gln	Ala	
	aga Arg															480
	caa Gln		-										-	-	-	528
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_	att Ile	_	_	_						_		_		•	_	624
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	Ile		20					25					30			
Jy S	116	35	JE1	ary	rie t	-	40	A I a	JE1	3C1	vai	45	LCU	vsh	L.CU	

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Val Glu Ser Gln Thr Glu Val Ser Ser Glu Tyr Ser Met Asp Lys Ala
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Met Val Glu Phe Ala Thr Leu Asp Arg Gln Leu Asn His Tyr Val Lys
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Ala Val Gln Ser Thr Ile Asn His Val Lys Glu Glu Arg Pro Glu Lys
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Ile Pro Asp Leu Lys Leu Leu Val Glu Lys Lys Phe Leu Ala Leu Gln
                                105
Ser Lys Asn Ser Asp Ala Asp Phe Gln Asn Asn Glu Lys Phe Val Gln
        115
                            120
                                                125
Phe Lys Gln Gln Leu Lys Glu Leu Lys Lys Gln Cys Gly Leu Gln Ala
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Asp Arg Glu Ala Asp Gly Thr Glu Gly Val Asp Glu Asp Ile Ile Val
                    150
                                        155
Thr Gln Ser Gln Thr Asn Phe Thr Cys Pro Ile Thr Lys Glu Glu Met
                                    170
Lys Lys Pro Val Lys Asn Lys Val Cys Gly His Thr Tyr Glu Glu Asp
                                185
Ala Ile Val Arg Met Ile Glu Ser Arg Gln Lys Arg Lys Lys Ala
                            200
                                                205
Tyr Cys Pro Gln Ile Gly Cys Ser His Thr Asp Ile Arg Lys Ser Asp
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Leu Ile Gln Asp Glu Ala Leu Arg Arg Ala Ile Glu Asn His Asn Lys
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									gtg Val				144
			-						gct Ala				192
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									aac Asn				336
	-		-		-				ctg Leu				384
		-	_	-					gtg Val				432
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		_	_							agg Arg		-	_	_	624
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	•	-			-	-	_			ggg Gly					720
	_			-	-					gac Asp	•	_		_	768
_			_	_				_	_	agc Ser				•	816
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Ala	Phe	Leu 35	Ala	Glu	Leu	Leu	Asn 40	Ser	Asn	Val	Ala	Asn 45	Asp	Leu	Met
Leu	Leu 50	Asp	Ser	Leu	Leu	G1u 55	Ser	Leu	Ala	Ala	Arg 60	Gln	Lys	Asp	Thr
Cys 65	Ala	Xaa	Val	Arg	Arg 70	Leu	Val	Leu	Arg	Gly 75	Leu	Ala	Asn	Leu	A1a 80
Ser	Gly	Cys	Pro	Asp 85	Lys	Val	Arg	Thr	His 90	Gly	Pro	Gln	Leu	Leu 95	Thr
Ala	Met	IJе	Gly 100	Gly	Leu	Asp	Asp	Gly 105	Asp	Asn	Pro	His	Ser 110	Pro	Val
Ala	Leu	G1u 115	Ala	Met	Leu	Gly	Leu 120	Ala	Arg	Leu	Val	His 125	Leu	۷al	Glu
Ser	Trp 130	Asp	Leu	Arg	Ser	Gly 135	Leu	Leu	His	Val	Ala 140	Ile	Arg	Ile	Arg
Pro 145	Phe	Phe	Asp	Ser	G1u 150	Lys	Met	Glu	Phe	Arg 155	Thr	Ala	Ser	Ile	Arg 160
			His	165		•			170	_	·	·		175	
			Gln 180			_		185					190		
		195	Gln				200				_	205			
	210		Pro			215					220				
225			Gln		230					235					240
			Lys	245					250					255	
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	T.rp	G1u 270	Asn	۷al
		275	Ala				280					285			
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											gga Gly					24	40
					-						ttg Leu					28	38
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								tgt Cys 330						1008
ccg Pro		-	_	 _	-	_			-	-		-	~ ~	1056
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				165					170					175		
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Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu	
Ser	Glu 210	Lys	Ala	Lys	Glu	Phe 215	Leu	Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe	
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235	Leu	Ser	Leu	Ala	Asn 240	
Gln	Pro	Val	Ile	His 245	Ser	Ala	Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255	Lys	
Asp	Thr	Thr	Ser 260	Lys	Ala	He	His	Ser 265	Пе	Phe	Lys	Asn	Ala 270	Ile	Gln	
	Leu	275					280					285			·	
Asn	Leu 290	Tyr	Tyr	Val	Thr	Arg 295	Glu	Asp	Lys	Asp	Leu 300	His	Arg	Lys	Пе	
His 305	Arg	He	Ile	Gln	G1n 310	Asp	Cys	Gln	Lys	Pro 315	Asn	His	Met	Glu	Lys 320	
	Cys			325					330					335		
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	_				-	-	_				agc Ser	•	_	336
			-	_							gac Asp 125	_		384
											gac Asp			432
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185

gtc agc aac gat ccc gat gtc atc aag ttg caa gag att cca acc ttc 96 Val Ser Asn Asp Pro Asp Val Ile Lys Leu Gln Glu Ile Pro Thr Phe

		20					25					30			
					cta Leu										144
				_	gac Asp 55					_	_		_		192
				-	cat His	-				-	-	-		_	240
	_	-	_		cga Arg				-	-	•		_	-	288
		_		_	cag Gln		_	_		-		-	-		336
Glu					gtg Val										384
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Ala Lys Leu Glu Lys Leu Asp Ser Gln Gln Val Leu Gln Leu Cys Leu
Arg Tyr Gln Asp His Leu His Gln Cys Ala Glu Ala Val Ala Phe Asp
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                                         75
Gln Asn Ala Leu Val Lys Arg Ile Lys Glu Met Asp Leu Ser Val Glu
Thr Leu Phe Ser Phe Met Gln Glu Arg Gln Lys Arg Tyr Ala Lys Tyr
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Ala Glu Gln Ile Gln Lys Val Asn Glu Met Ser Ala Ile Leu Arg Arg
        115
                            120
                                                 125
Ile Gln Met Gly Ile Asp Gln Thr Val Pro Leu Leu Asp Arg Leu Asn
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Asp Arg Glu Leu Arg Leu
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cta gca gca gat ccg tta aac aga aga gcc atc gtc cag gat cag gga
                                                                       96
Leu Ala Ala Asp Pro Leu Asn Arg Arg Ala Ile Val Gln Asp Gln Gly
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			_		ctt Leu	_				-	_	-		-	336
			-		tca Ser					_				-	384
					gcc Ala 135					-			-		432
-	-	-			aga Arg			-	-			-			480
					ttt Phe				_	-	_			-	528
					gat Asp										576
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Ser Glu Ile Tyr Asp Ile Leu Gln Ser Ser Asn Met Ala Asp Gly Asp
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Ser Phe Asn Glu Met Asn Ser Arg Arg Lys Ala Xaa Phe Phe Leu
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Gly Thr Thr Asn Lys Arg Ala Lys Thr Val Val Leu His Ile Asp Gly
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							ttt Phe		-		agg Arg 160	480
							tcg Ser			_		528
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							gag Glu					624
							cca Pro 220					672
							gta Val					720
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Pro Phe Asn Pro Trp Asn Trp Gly Lys Leu Ala Glu Ala Tyr Leu Asn 50 55 60

Leu Gly Pro Ala Leu Ser Ala Ala Leu Ala Ser Ser Gln Lys Gln His 65 70 75 80

Ser Phe Thr Ser Ser Asp Lys Thr Ile Lys Ser Phe Phe Pro His Ser 85 90 95

Gly Lys Asp Cys Leu Leu Cys Phe Pro Glu Thr Leu Pro Glu Ser Ser 100 105 110

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Val Gly Ser Val Ala Leu Thr Ala Leu Val Thr Val Ser Ser Glu Glu 225 230 235 240

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Ser Gln Asp Tyr Leu Glu Leu Ala Asn Arg Phe Pro Gln Gln Ala Trp
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Gly Leu Pro Gly Ala Trp Gly Lys Leu Ala Thr Phe Asn Ser Trp Tyr
Leu Phe Asn Ser Val Ala Phe Gln Asn Ala Asp Ala Thr Arg Arg Thr
Cys Pro Gln Leu Thr Thr Tyr Gly Cys His Gly Ser Gly Gln Leu Ser
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Lys Gln Val Pro Val Val Ser Ser Ala Val
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ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
             20
gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
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Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
                             40
                                                 45
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cta Leu 50												192
cga Arg												240
gag Glu										_		288
 aag Lys	 	-	-		-	-				_	_	336
gat Asp				-					-			384
tgg Trp 130												432
ccc Pro												480
tgc Cys												528
ggc Gly											-	576
ggc Gly	-					_				-	_	624
agg Arg 210												672

				gcc Ala												720
			-	tac Tyr 245										_		768
	-		-	ggc Gly				-			_		 	_		816
	-			agc Ser		_		-			-	-		-		864
	-	-		gat Asp	-	-				-			_	_		912
		-		aga Arg		_		-	-				-			960
_				aac Asn 325		_					_				1	1008
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Pro	Leu	Trp	Ser 20	Ser	Ser	Leu	Pro	Gly 25	Leu	Asp	Thr	Ala	Glu 30	Ser	Lys
Ala	Thr	Ile 35	Ala	Asp	Leu	Ile	Leu 40	Ser	Ala	Leu	Glu	Arg 45	Ala	Thr	۷a٦
Phe	Leu 50	Glu	Gln	Arg	Leu	Pro 55	Glu	Ile	Asn	Leu	Asp 60	Gly	Met	Val	Gly
Val 65	Arg	Val	Leu	Glu	G1u 70	Gln	Leu	Lys	Ser	Va1 75	Arg	Glu	Lys	Trp	Ala 80
Gln	Glu	Pro	Leu	Leu 85	Gln	Pro	Leu	Ser	Leu 90	Arg	Val	Gly	Met	Leu 95	Gly
			100		Ala			105				-	110	-	
	·	115	-		Leu		120					125			
	130	_			His	135	•				140		•		
145				_	Pro 150					155					160
				165	Leu				170					175	
-			180	•	Leu	•	_	185				-	190	•	-
		195			Ser		200					205	·		3
	210	-			Gln	215					220				
225					Asn 230					235					240
Пe	Gly	Tyr	Ala	Tyr 245	Pro	Thr	Arg	Asp	11e 250	Phe	Met	Glu	Asn	11e 255	Met
Phe	Cys	Gly	Met 260	Gly	Gly	Phe	Ser	Asp 265	Phe	Tyr	Lys	Leu	Arg 270	Trp	Leu
Glu	Ala	Ile 275	Leu	Ser	Trp	Gln	-		Gln		Gly	Cys 285	Phe	Gly	Glu
Pro	Asp 290	Ala	Glu	Asp	Glu	G1u 295	Ser	Ser	Lys	Ala	Ile 300	Gln	Tyr	Gln	Gln
His 305	Phe	Ser	Arg	Arg	Val 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	Gly 320
Cys	Ser	Ser	His	Asn 325	Thr	Ala	Thr	Ala	Val 330	Ala	Ala	Leu	Gly	Gly 335	Phe
Leu	Tyr	Ile	Leu 340	Ala	Glu	Tyr	Pro	Pro 345	Ala	Asn	Arg	Glu	Pro 350		Pro

Ser	Thr	Pro 355		Pro	Pro	Ser	Ser 360	-						
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	Asn	Gly	Leu	Ser	gag Glu 70	Glu	Lys	Pro	Leu	Ser	Val			240
					acc Thr									288
					gag Glu									336

							tac Tyr 125			384
							ctg Leu			432
							ctg Leu			480
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							gag Glu			576
							cag G1n 205			624
	_	_					cct Pro		 -	672
							gtg Val			720
							cac His			768
							ctc [.] Leu			816
Phe			Phe				aca Thr 285			864

		Asp				cag G1n 295	Pro					Thr				912
ctg Leu 305	ctg Leu	tcc Ser	gat Asp	tct Ser	gcc Ala 310	ttc Phe	gac Asp	tct Ser	999 Gly	cgc Arg 315	ctc Leu	tgg Trp	ttg Leu	ctg Leu	gtg Val 320	960
						ctg Leu										1008
						gcc Ala										1056
						gaa Glu										1104
						agc Ser 375										1152
						ctg Leu										1200
			Pro			cta Leu										1248
						ggg Gly										1296
cgg Arg	Ile					Gly										1344
ggc Gly					Leu					Ala						1392

gcc agc ctt ttc ggc ctc tac ttc cac cag cac ttg gca ggc tcc tag 1440 Ala Ser Leu Phe Gly Leu Tyr Phe His Gln His Leu Ala Gly Ser * 470 <210> 318 <211> 479 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(479) <223> Xaa = Any Amino Acid <400> 318 Met Ala Val Leu Gly Val Gln Leu Val Val Thr Leu Leu Thr Ala Thr 10 Leu Met His Arg Leu Ala Pro His Cys Ser Phe Ala Arg Trp Leu Leu Cys Asn Gly Ser Leu Phe Arg Tyr Lys His Pro Ser Glu Glu Glu Leu 40 Arg Ala Leu Ala Gly Lys Pro Arg Pro Arg Gly Arg Lys Glu Arg Trp 55 Ala Asn Gly Leu Ser Glu Glu Lys Pro Leu Ser Val Pro Arg Asp Ala 75 Pro Phe Gln Leu Glu Thr Cys Pro Leu Thr Thr Val Asp Ala Leu Val 90 Leu Arg Phe Phe Leu Glu Tyr Gln Trp Phe Val Asp Phe Ala Val Tyr 105 Ser Gly Gly Val Tyr Leu Phe Thr Glu Ala Tyr Tyr Met Leu Gly 120 125 Pro Ala Lys Glu Thr Asn Ile Ala Val Phe Trp Cys Leu Leu Thr Val 130-135 140 Thr Phe Ser Ile Lys Met Phe Leu Thr Val Thr Arg Leu Tyr Phe Ser 150 155 Ala Glu Glu Gly Glu Arg Ser Val Cys Leu Thr Phe Ala Phe Leu 170 Phe Leu Leu Ala Met Leu Val Gln Val Val Arg Glu Glu Thr Leu 185 Glu Leu Gly Leu Glu Pro Gly Leu Ala Ser Met Thr Gln Asn Leu Glu 200

Pro Leu Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys

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Phe 1	Leu	Thr	Phe	Pro 245	Gly	Leu	Arg	Leu	Ala 250	Gln	Thr	His	Arg	Asp 255	Ala
Leu	Thr	Met	Ser 260	Glu	Asp	Arg	Pro	Met 265	Leu	Gln	Phe	Leu	Leu 270	His	Thr
Ser	Phe	Leu 275	Ser	Pro	Leu	Phe	Ile 280	Leu	Trp	Leu	Trp	Thr 285	Lys	Pro	Ile
Ala	Arg 290	Asp	Phe	Leu	His	G1n 295	Pro	Pro	Phe	Gly	G1u 300	Thr	Arg	Phe	Ser
Leu   305	Leu	Ser	Asp	Ser	Ala 310	Phe	Asp	Ser	Gly	Arg 315	Leu	Trp	Leu	Leu	Val 320
Val I	Leu	Cys	Leu	Leu 325	Arg	Leu	Ala	Val	Thr 330	Arg	Pro	His	Leu	G1n 335	Ala
Tyr I	Leu	Cys	Leu 340	Ala	Lys	Ala	Arg	Val 345	Glu	Gln	Leu	Arg	Arg 350	Glu	Ala
Gly /	Arg	I Te 355	Glu	Ala	Arg	Glu	Ile 360	Gln	Gln	Arg	Val	Val 365	Arg	Val	Tyr
Cys (	Tyr 370	Val	Thr	Val	Val	Ser 375	Leu	G1n	Tyr	Leu	Thr 380	Pro	Leu	Ile	Leu
Thr 1 385	Leu	Asn	Cys	Thr	Leu 390	Leu	Leu	Lys	Thr	Leu 395	Gly	Gly	Tyr	Ser	Trp 400
Gly I	Leu	Gly	Pro	Ala 405	Pro	Leu	Leu	Ser	Pro 410	Asp	Pro	Ser	Ser	Ala 415	Ser
Ala 7	Ala	Pro	Ile 420	Gly	Ser	Gly	Glu	Asp 425	Glu	Val	Xaa	Gln	Thr 430	Ala	Ala
Arg :		A1a 435	Gly	Ala	Leu	Gly	Gly 440	Leu	Leu	Thr	Pro	Leu 445	Phe	Leu	Arg
Gly V	Val 450	Leu	Ala	Tyr	Leu	Ile 455	Trp	Trp	Thr	Ala	A1a 460	Cys	Gln	Leu	Leu
Ala 5 465	Ser	Leu	Phe	Gly	Leu 470	Tyr	Phe	His	G1n	His 475	Leu	Ala	Gly	Ser	

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							gaa Glu										192
							cat His									٠	240
		-					gag Glu										288
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Lys	Ala	Leu 35	Phe	Thr	Tyr	Pro	Lys 40	Gly	Ala	Gly	GTu	Met 45	Leu	Glu	Asp		
Gly	Ser 50	-	Arg	Phe	Leu	Cys 55	Glu	Ser	Val	Phe	Ser 60		Gln	Val	Ala		
Ser		Leu	Lys	Gln	Val		His	Asp	Gln	Gln	-	Ala	Arg	Met	Glu		

65 Lys	Leu	Ala	Gly	Leu 85	70 Val	Glu	Glu	Leu	G1u 90	75 Ala	Asp	Glu	Trp	Arg 95	80 Phe		
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										gcc Ala							96
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		Ser				Gly		Gln	Ser	aat Asn							192
										agt Ser 75							240
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					aca Thr							-		-	336
					gta Val						-		-		384
	-				cct Pro 135										432
	_				ggt Gly	-			_					-	480
	_		-	-	cag Gln					-	-	-		_	528
	_				cca Pro	_			_	_	-	-			576
-	-		-		tct Ser	-		-							624
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	-	_			gga Gly	_				_		-	-		720
					atg Met										768
					gct Ala						-		_		816

			_							atc Ile			-		864
										cgg Arg 300					912
										aaa Lys					960
		_			_					gat Asp	_		-		1008
										gcc Ala			Leu		1056
	-	_	_		_					gag Glu					1104
	-		-					-		atg Met 380			_		1152
										atg Met					1200
	Glu	Pro	Trp	Lys	Glu	Gln	Thr	Gln	Lys	ttc Phe	He	Asp	Trp	Leu	1248
										tca Ser					1296
	-				-					gtt Val					1344

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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
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Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
            100
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
                        135
                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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                                        155
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Ala Leu Leu
                                    170
                165
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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                                185
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Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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.215

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Lys Ala Ala Ser Pro Leu Gly Ser Pro Glu Leu Cys Pro Ser Ala Leu
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                                        235
His Gly Leu Ser Gln Ala Met Lys Leu Pro Ser Pro Ala His His Leu
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                245
Trp Ser Leu Leu Ser Glu Ala Thr Gly Lys Ile Phe Asp Leu Leu Pro
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Asn Lys Ile Arg Arg Lys Asp Leu Glu Leu Tyr Ile Ser Ile Ala Lys
                            280
Cys Leu Leu Glu Met Thr Asp Asp Asp Ala Asn Arg Ile Ala Gln Val
                        295
                                            300
Thr Lys Ser Asn Ile Glu Lys Ala Ala Phe Val Lys Leu Tyr Leu Val
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                                        315
Ser Gln Gly Arg Phe Pro Leu Val Asn Leu Thr Asp Met Leu Arg Phe
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                                    330
Ala Thr Ala Val Val Ala Trp Ala Asp His Thr Ala Pro Leu Leu Leu
                                345
Gly Leu Ser Ala Ser Trp Leu Pro Trp His Gln Glu Asn Gly Pro Ala
                            360
Gly Pro Val Pro Ser Phe Leu Gly Arg Ser Pro Met His Arg Val Thr
                        375
                                            380
Leu Gln Glu Val Leu Thr Leu Leu Pro Asn Ser Met Ala Leu Leu Leu
                    390
Gln Lys Glu Pro Trp Lys Glu Gln Thr Gln Lys Phe Ile Asp Trp Leu
                405
                                    410
Phe Ser Ile Met Glu Ser Pro Lys Glu Ala Leu Ser Ala Gln Ser Arg
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Asp Leu Leu Lys Ala Thr Leu Leu Ser Leu Arg Val Leu Pro Glu Phe
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Lys Lys Lys Ala Val Trp Thr Arg Ala Tyr Gly Trp
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						_							_	gtc Val		144
_	=							-			-	-		ctt Leu		192
												-	-	gcc Ala		240
-			-		-									gga Gly 95	_	288
														tct Ser		336
						-								gtt Val		384
														tct Ser		432
														ctt Leu		480
	-	-		~		-			_		_	-	-	cta Leu 175	_	528

										agt Ser	_					576
	_			_						tgg Trp						624
_	_	_		_			-			tta Leu	_		-	_		672
	-									cta Leu 235	_		-	-		720
		_	-	-	-	-		_		agc Ser		-				768
	-	-			-	_				att Ile		-		_		816
						-				tat Tyr						864
-			_	_		-	-	_	-	aat Asn			_	-	_	912
		-			-		-	-		gtc Val 315		-			-	960
			_			_			_	acc Thr		_	. –	-		1008
-		-		-	-		- •	-	_	gcc Ala		•		_		1056

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_	_	_				-		_	-				-	aat Asn	•	1152
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	-	_		_	-	_	_						-	cag Gln		1440
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														ctg Leu		1536
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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
                        55
                                            60
Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
               85
                                    90
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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                                                125
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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                        135
                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
               165
                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
                                185
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265	Lys	Ile	Phe	Asp	Leu 270	Leu	Pro
Asn	Lys	Ile 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Ile	Ser 285	Пe	Ala	Lys
Cys	Leu 290	Leu	Glu	Met	Thr	Asp 295	Asp	Asp	Ala	Asn	Arg 300	Ile	Ala	Gln	۷a۱
305					310	-			Phe	315	•		_		320
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			340					345	Leu				350		
		355					360		His			365	_		
	370					375			Met		380		_		
385					390				Thr	395		·			400
Asp	Phe	Phe	Leu	Leu 405	Ile	Phe	Ala	Thr	Ala 410	Val	Val	Ala	Trp	Ala 415	Asp
His	Thr	Ala	Pro 420	Leu	Leu	Leu	Gly	Leu 425	Ser	Ala	Ser	Trp	Leu 430	Pro	Trp
His	Gln	G1u 435	Asn	Gly	Pro	Ala	Gly 440	Pro	Val	Pro	Ser	Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	Gln	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
Asn 465	Ser	Met	Ala	Leu	Leu 470	Leu	Gln	Lys	Glu	Pro 475	Trp	Lys	Glu	Gln	Thr 480
Gln	Lys	Phe	Ile	Asp 485	Trp	Leu	Phe	Ser	Ile 490	Met	Glu	Ser	Pro	Lys 495	Glu
Ala	Leu	Ser	Ala. 500	Gln	Ser	Arg	Asp	Leu 505	Leu	Lys	Ala	Thr	Leu 510	Leu	Ser
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													tcg Ser		240
													gcc Ala 95		288
					_						-	-	gac Asp	_	336
												_	ttc Phe		384
													atg Met		432

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			acc Thr													480
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			cgg Arg						_							624
			999 Gly				-	-			-	-	tga *			666
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Trp	Val	Arg	Gly 20	Ser	Gly	Pro	Ser	Va1 25	Leu	Ser	Arg	Leu	Gln 30		Ala	
Ala	Val	Val	Arg	Pro	Gly	Phe	Leu		Thr	Ala	Glu	Glu		Thr	Leu	

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Trp Val Arg Gly Ser Gly Pro Ser Val Leu Ser Arg Leu Gln Asp Ala 20 25 30

Ala Val Val Arg Pro Gly Phe Leu Ser Thr Ala Glu Glu Glu Thr Leu 35 40 45

Ser Arg Glu Leu Glu Pro Glu Leu Arg Arg Arg Arg Tyr Glu Tyr Asp 50 55 60

His Trp Asp Ala Ala Ile His Gly Phe Arg Glu Thr Glu Lys Ser Arg 65 70 75 80

Trp Ser Glu Ala Ser Arg Ala Ile Leu Gln Arg Val Gln Ala Ala Ala 85 90 95

Phe Gly Pro Gly Gln Thr Leu Leu Ser Ser Val His Val Leu Asp Leu 100 105 110

Glu Ala Arg Gly Tyr Ile Lys Pro His Val Asp Ser Ile Lys Phe Cys 115 120 125

Gly Ala Thr Ile Ala Gly Leu Ser Leu Leu Ser Pro Ser Val Met Arg

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Pro	Arg	Gly 195		Arg	Ile	Ser	Val -200	Ile	Cys	Arg	Ser	Leu 205		Glu	Gly	
Met	Gly 210	Pro	Gly	Glu	Ser	Gly 215	Gln	Pro	Pro	Pro	A1a 220	Cys				
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ctt Leu 65	ata Ile	aaa Lys	gcc Ala	tta Leu	aag Lys 70	gac Asp	att Ile	aaa Lys	gtg Val	ggc Gly 75	ttt Phe	gta Val	aag Lys	atg Met	gag Glu 80	240
tca Ser	gtg Val	gaa Glu	gaa Glu	ttt Phe	gaa Glu	ggt Gly	ttg Leu	gat Asp	tct Ser	ccg Pro	gaa Glu	ttt Phe	gaa Glu	atg Met	tat Tyr	288

85 90 95

ttg tag
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<210> 328

<211> 97

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<213> Homo sapiens

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Leu

<210> 329

<211> 270

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ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg 96 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

20 25 30 tgg aag ata aac aac ctc att gcc tca gaa tcc tac tac acc tac gcc 144 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 35 40 tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg 192 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 50 55 60 ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag 240 Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 gaa gcc gtg gag aga cag ttg atg acc tga 270 Glu Ala Val Glu Arg Gln Leu Met Thr * 85

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Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg 20 25 30

Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala

5 40 48

Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 50 55 60

Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 70 75 80

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85

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<210> 332

<211> 84

<212> PRT

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<400> 332

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Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Ser Phe Ser Asp 50 55 60

Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln

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	Phe Leu Asn His Le	tt acc tcc ttc aag gaa eu Thr Ser Phe Lys Glu 40 45	-
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<211> 80

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<213> Homo sapiens

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Ala	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	Glu 45	Ser	Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	Glu 60	Ala	Leu	Ser	Asn	
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	gtt Val															96
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	gat Asp 50															192
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									ttt Phe					-	_		384
			-						gcc Ala								432
_	_	-	-		-				cag Gln			-	-	-		٠	480
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1				5	·				10					15			
He	Leu	Ala	Val 20	Phe	lyr	Pro	Phe	Va1 25	Asp	Leu	He	Asp	Asn 30	Phe	Asn		
Gln	Thr	His 35	Lys	Tyr	Ala	Pro	Phe 40	Ile	He	Пe	Gly	Leu 45	His	Leu	Ala		
Leu	Gly		Phe	Ser	Phe	Thr		Asp	Thr	Trp	Ser		Ser	Arg	Gly		

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Asp 65		Ala	Glu	Ile	Leu 70	Gly	Ser	Gly	Ala	Gly 75		Ala	Cys	Gly	Ser 80	
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Пe	Leu		100 Ile	Leu	Ile	Gly		105 Val	Phe	۷a٦	Leu		110 Ile	Arg	Asp	
Val		115 Lys	Lys	Ile	Thr	Ile	120 Pro	Leu	Ala	Cys	Lys 140	125 Ile	Phe	Asn	Ile	
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						gtc Val										96
_		-	_			gcg Ala										144
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490

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aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg 192 Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp 50 55 60 cat tcg gga tat ggc tcc ctg gcc agc ttg tga 225 His Ser Gly Tyr Gly Ser Leu Ala Ser Leu * 65 <210> 342 <211> 74 <212> PRT <213> Homo sapiens <400> 342 Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro 5 10 15 Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg 25 Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp 55 His Ser Gly Tyr Gly Ser Leu Ala Ser Leu 65 70 <210> 343 <211> 240 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(240) <400> 343 atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc 48 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 10 atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca 96 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 20 25 30

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ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile * 70 75 65 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 25 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 70 75 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg 48 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 5 10 15

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												ccc Pro		144
				-		_	-		-		_	aac Asn		192
										-	_	act Thr		240
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<213> Homo sapiens

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 Gln Asp Ala Ser Ser Asp Gln Arg Pro 25
 Val Val Pro Ser Ser Arg Ser 30

 Arg Phe Ala Phe Ser Val Ser Val Leu Asp Leu Asp Leu Lys Pro Tyr 35
 40
 45

 Glu Ser Ile Pro His Gln Tyr Lys Leu Asp Gly Lys Ile Val Asn Tyr 50
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 Tyr Ser Lys Thr Val Arg Ala Lys Asp Asn Ala Val Met Ser Thr Arg 65
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 Phe Lys Glu Ser Glu Asp Cys Thr Leu Val Leu His Lys Val

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<211> 474

<212> DNA

<213> Homo sapiens

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495

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-			_		_	-	_		cta Leu				96
									ggt Gly				144
		-					-		gat Asp 60			-	192
	-	-		-		-			gct Ala	_	_		240
									ctt Leu			tga *	288

<210> 350

<211> 95

<212> PRT

<213> Homo sapiens

<400> 350

 Met
 Ala
 Lys
 Ala
 Leu
 Ile
 Val
 Ile
 Phe
 Ser
 Ser
 His
 Leu
 Arg
 Pro
 Ile

 Glu
 Leu
 Phe
 Ser
 Ser
 Arg
 Lys
 Val
 Leu
 Phe
 Leu
 Ser
 Gln
 Lys
 Trp

 Ala
 Ser
 Asn
 Asn
 Gln
 Ser
 Arg
 Ser
 Val
 Ala
 Val
 Gly
 Lys
 Met
 Val
 Asp

 Arg
 His
 Gln
 Ser
 Tyr
 Phe
 Leu
 Ile
 Cys
 Pro
 Val
 Gly
 Lys
 Met
 Val
 Asp
 Glu
 Trp
 Asn
 Cys

 Gly
 Thr
 Ser
 Asp
 Val
 Glu
 Leu
 Met
 Gly
 Ala
 Thr
 Ala
 Val
 Gln
 Thr
 Ile

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96

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tta ctt ctc tgt gcc ctg gag ccc ctc aag cac aga ggc ctc gaa agg
Leu Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
             20
                                 25
ttg atc aga cat cct cag cac ctg gag cgg ggc ctg gca cac aag acg
Leu Ile Arq His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
         35
gca atg aac ggc caa ccc tag
Ala Met Asn Gly Gln Pro *
     50
      <210> 352
      <211> 54
      <212> PRT
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Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala
Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg
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Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr
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1
                 5
                                                          15
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                       96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
                                 25
             20
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
                                                                      144
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
                             40
                                                  45
                                                                      159
cgt gtc ggg ctt tga
Arg Val Gly Leu *
     50
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      <211> 52
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      <400> 354
Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
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Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
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Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
        35
                            40
Arg Val Gly Leu
    50
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	tta Leu																96
uiy	LCU		20	,	mu	1,31	L) J	25	uij	001	,	, · ·	30	,,,	1113		
	atg	_	-			-											144
Phe	Met	Asp 35	Ala	Glu	Leu	Cys	Ser 40	Gln	Tyr	Trp	Thr	Lys 45	Trp	Leu	Leu		
	cta																192
Arg	Leu 50	Glu	Glu	lyr	ihr	55	Lys	Lys	Lys	Asn	60 60	Asn	He	Gin	Lys		
	gaa			-													210
65	Glu	ıyr	zer.	GIU	*												
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Gly	Leu	Ile	Val 20	Val	Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His		
	Met	35					40					45					
Arg	Leu 50	Glu	Glu	Tyr	Thr	G1u 55	Lys	Lys	Lys	Asn	Gln 60	Asn	Ile	Gln	Lys		
Pro 65	Glu	Tyr	Ser	Glu													
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1
                                     10
                 5
                                                                       96
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
             20
tte acg etc tet gat gge gtg etg gee tgg gae ace tte gee eag eec
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
                             40
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                         55
                                                                      240
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
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Met 1	Val	Leu	Pro	Va 1 5	Ala	Ala	lyr	Xaa	Leu 10	He	Leu	Met	Ala	Met 15	Leu		
Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Ala	Gly	Trp	Gly	A1a 30	Leu	Leu		
Phe	Thr	Leu 35		Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45		Gln	Pro		
Leu	Pro 50		Ala	Arg	Leu	Va1 55		Met	Thr	Thr	Tyr 60		Ala,	Ala	Gln		
Leu 65	Leu	Ile	Thr	Leu	Ser 70		Leu	Arg	Ser	Pro 75		Pro	Lys	Thr	Asp 80		
	<2 <2	210> 211> 212> 213>	324	o sap	oiens	5											
	<2	220> 221> 222>	CDS	(3	324)												
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	aag Lys																48
	gca Ala																96
	ccg Pro	-		-												]	L44
	cga Arg 50															1	192
	gcc Ala															2	240
agt	tgg	gca	gga	aga	ctc	att	ctg	agt	gta	gat	ggc	tct	ggg	ttt	tgt	2	288

PCT/US00/29052

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Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                 85
                                                          95
                                                                      324
gag agg gtg aaa tot ttg gto gtt aaa caa tto tag
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
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Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                85
                                    90
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
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      <211> 252
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(252)
      <400> 361
atg gag gaa ggc ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
                                                                      48
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                 5
                                     10
                                                         15
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
                                                                      96
```

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	G1 <i>y</i> 30	Gly	Arg		
-				ctc Leu	-	-					-	· .				:	144
				tct Ser	-									-	_		192
		-		atg Met			-			-						2	240
	aaa Lys		_													ź	252
	*	210	262														

<210> 362 <211> 83 <212> PRT <213> Homo sapiens

<400> 362

 Met Glu Glu Gly Gly Gly Gly Val Arg
 Ser Leu Val Pro Gly Gly Pro 1

 1
 5

 Val Leu Leu Val Leu Cys Gly Leu Leu Glu Ala Ser Gly Gly Gly Arg 20

 Ala Leu Pro Gln Leu Ser Asp Asp Asp Ile Pro Phe Arg Val Asn Trp Pro 35

 Gly Thr Glu Phe Ser Leu Pro Thr Thr Gly Val Leu Tyr Lys Glu Asp 50

 Asn Tyr Val Ile Met Thr Thr Ala His Lys Glu Lys Tyr Lys Lys Lys 65

 Lys Lys Asn

<210> 363

<211> 459

<212> DNA

<213> Homo sapiens

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<210> 364
      <211> 152
      <212> PRT
      <213> Homo sapiens
      <400> 364
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Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
                                25
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro
                            40
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
                                        75
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
                                    90
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
            100
                                105
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
                        135
                                            140
Phe Gly Glu Val Lys Ser Cys Leu
145
                    150
      <210> 365
      <211> 600
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(600)
      <400> 365
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                                                                       48
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
1
                                                                       96
ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
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Phe	Gly	Leu	Ser 20	Leu	Val	Tyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	Glu		
														cat His			144
			_				_			-			-	agt Ser	_		192
		•	_	-	-						_			atc Ile	-		240
														aat Asn 95			288
													-	gat Asp			336
												_	-	tcc Ser	-		384
					_						-			aac Asn			432
			-		-						-		-	cac His		1	480
													_	cag Gln 175			528
									Lys					gaa Glu	-		576
ccg	ccc	gag	ctc	ttc	ccc	gct	tga		•								600

Pro Pro Glu Leu Phe Pro Ala * 195

<210> 366

<211> 199

<212> PRT

<213> Homo sapiens

<400> 366

Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val 1 5 10 15

Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu 20 25 30

Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn 35 40 45

Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg 50 55 60

Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr 65 70 75 80

Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly 85 90 95

Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
100 105 110

Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys 115 120 125

Cys Leu Gln Pro Asn Lys Gln Leu Leu Leu Glu Arg Phe Leu Asn Arg 130 135 140

Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe 145 150 155 160

Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His 165 170 175

Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser 180 185 190

Pro Pro Glu Leu Phe Pro Ala

195

<210> 367

<211> 249

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(249)

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<210> 368

<211> 82

Ser Gly *

<212> PRT

<213> Homo sapiens

<400> 368

 Met Ser Lys Tyr Lys His Lys Ser Ser Pro Leu Leu Pro Leu Leu Ile

 1
 5
 10
 15

 Phe His Asn Val Cys Phe Ser Pro Ala Asn Lys Pro Lys Ile Leu Ala 20
 25
 30

 Asn Glu Lys Val Ile Thr Val Leu Ala Ala Cys Leu Glu Ser Glu Asn 35
 40
 45

 Gln Asn Ala Gln Arg Ile Gly Ala Ala Ala Leu Gly Ser Asp Leu Gln 50
 55
 60

 Leu Ser Glu Gly Lys Asn Ser Phe Glu Lys Pro Ile Ser Lys Lys Asp Ser Asp Leu Glo 70
 75
 80

Ser Gly

<210> 369 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 369 atg gac ggc cgc ggg gct ttc tgg aca gtg gcc att ccc aga gcc agg 48 Met Asp Gly Arg Gly Ala Phe Trp Thr Val Ala Ile Pro Arg Ala Arg cag gaa ggc ctc ggg agg ctg ggg ctc ccg ttc ccg gtg aag cgg acg 96 Gln Glu Gly Leu Gly Arg Leu Gly Leu Pro Phe Pro Val Lys Arg Thr 20 ccg cca gcg ccc cag aac cca gga gga agc aca cag gcc cca cag aga 144 Pro Pro Ala Pro Gln Asn Pro Gly Gly Ser Thr Gln Ala Pro Gln Arg 35 40 gtg gtt ggc aag agt cac tcg ggg att agg atg ccg gcc aaa tcg cgg 192 Val Val Gly Lys Ser His Ser Gly Ile Arg Met Pro Ala Lys Ser Arg 50 55 aat ttg agg ctg gaa tcc aag ctc aac agg act gct gtg tgt gaa gca 240 Asn Leu Arg Leu Glu Ser Lys Leu Asn Arg Thr Ala Val Cys Glu Ala 65 70 75 80 ctc aag agg gcc cct aca acc aac ctg cca gga gtc ggc tcc tga 285 Leu Lys Arg Ala Pro Thr Thr Asn Leu Pro Gly Val Gly Ser * 85 90

<210> 370

<211> 94

<212> PRT

<213> Homo sapiens

<400> 370

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Gln	Glu	Gly	Leu 20	Gly	Arg	Leu	Gly	Leu 25	Pro	Phe	Pro	۷a٦	Lys 30	Arg	Thr	
Pro	Pro	Ala 35	Pro	Gln	Asn	Pro	Gly 40	Gly	Ser	Thr	Gln	Ala 45	Pro	Gln	Arg	
Val	Va1 50	Gly	Lys	Ser	His	Ser 55	Gly	Ile	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
Asn 65	Leu	Arg	Leu	Glu	Ser 70	Lys	Leu	Asn	Arg	Thr 75	Ala	Val	Cys	G1u	Ala 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 90	Gly	Val	Gly	Ser			
	<2 <2			o sap	oiens	5										
	<2	220> 221> 222>	CDS	(2	249)											
	<4	100>	371													
	cgc Arg	gac	tgc	-			-				_		_	-		48
	ttg Leu															96
	ctc Leu													-	-	144
	gac Asp 50															192
	agg Arg															240
65	-				70					75					80	÷
ccg	aga	tga														249

96

Pro Arg *

<210> 372

<211> 82

<212> PRT

<213> Homo sapiens

<400> 372

Met Arg Asp Cys Asp Ile Asn Asp Asp Glu Phe Leu His Leu Pro Ala 1 5 10 15

His Leu Arg Val Val Gly Pro Gln Gln Leu His Ser Glu Thr Asn Glu 20 25 30

Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35 40 45

Val Asp Gln Ala Leu Trp Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50 55 60

Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65 70 75 80

Pro Arg

<210> 373

<211> 219

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(219)

<221> misc feature

<222> (1)...(219)

<223> n = A,T,C or G

<400> 373

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nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc tca gcc cat Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His 20 25 30

	gca Ala		Leu													144
	.ccc Pro 50															192
	acc Thr			-				tag *								219
	<2 <2	210> 211> 212> 213>	72 PRT	o sar	oiens	S			•					-		
	<2 <2	222>	VAR] (1). Xaa	(7		nino	Acid	d								
Met	<4 Gly	100> Arg		Leu	Pro	Pro	Gly	Gly	Pro	Arg	Arg	Arg	Ala	Xaa	Leu	
1 Xaa	Ala	Xaa		5 A <b>l</b> a	Gly	Ser	Ile		10 Glу	Arg	Arg	Arg		15 Ala	His	
Tyr	Ala	Asn 35	20 Leu	Ala	Gly	Pro	Thr 40	25 Asn	Pro	Ala	Leu	Pro 45	30 Pro	Leu	Leu	
Glu	Pro 50		Arg	Arg	Ala	Cys 55		Leu	Arg	Ala	Leu 60		Gly	Ala	Gly	
Asn 65	Thr	Thr	His	Cys	Pro 70	Phe	Ala									
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	<2	?20> ?21>		(5	70)											

	gcc	ccc		-						ctg Leu			-	48
				-					-	aca Thr	-		-	96
-				-	-		_		-	ttg Leu 45	-	_		144
			_							tgc Cys		-		192
_			-		_				_	gcc Ala		-		240
		-			_	-		_	-	ctc Leu	•			288
										cct Pro			-	336
										gtg Val 125				. 384
										tgg Trp				432
										gag Glu				480
										ttg Leu				528

165 170 175

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag 576 Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu 180 185 190

tga 579

<210> 376

<211> 192

<212> PRT

<213> Homo sapiens

<400> 376

Met Ala Pro Lys Pro Gly Ala Glu Trp Ser Thr Ala Leu Ser His Leu 1 5 10 15

Val Leu Gly Val Val Ser Leu His Ala Ala Val Ser Thr Ala Glu Ala 20 25 30

Ser Arg Gly Ala Ala Ala Gly Phe Leu Leu Gln Val Leu Ala Ala Thr 35 40 45

Thr Thr Leu Ala Pro Gly Leu Ser Thr His Glu Asp Cys Leu Ala Gly 50 55 60

Ala Trp Val Ala Thr Val Ile Gly Leu Pro Leu Leu Ala Phe Asp Phe 65 70 75 80

His Trp Val Asn Gly Asp Arg Ser Ser Ala Asn Leu Leu Gly Gly 85 90 95

Gly Met Val Leu Ala Val Ala Gly Gly His Leu Gly Pro Glu Gly Arg 100 105 110

Ser Val Ala Gly Gln Ala Met Leu Leu Val Val Ala Val Thr Ile Leu

Ile Val Ala Val Phe Thr Ala Asn Thr Tyr Gly Met Trp Gly Gly Ala 130 135 140

Met Leu Gly Val Ala Gly Leu Leu Ser Arg Leu Glu Glu Asp Arg Leu 145 150 155 160

Leu Leu Pro Lys Glu Asp Val Cys Arg Trp Ala Leu Ala Val Gly 165 170 175

Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu 180 185 190

<210> 377

<211> 606

		DNA Hom	o saj	pien	S									
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					gtg Val	-					 	_	96	•
	-		-		cgc Arg					_	 		144	
					acc Thr 55						 -	-	192	•
					cat His								240	
					gag Glu								288	
_	-	-	-	-	aac Asn	_	 _	•	-			_	336	
					ctg Leu								384	
-					gag Glu 135	-		-	-	_		-	432	

	Ser												-	att Ile		480
														gcc Ala 175	-	528
	_	_	_	-		-	_							tcc Ser		576
	999 Gly								tga *							606
	<; <;	210> 211> 212> 213>	201 PRT	saj	oiens	5										
	_	400.														
Met			378 Gln	Ara	Leu	Val	Ala	Ala	Ala	Val	Leu	Val	Ala	Leu	Val	
' 1	Thr	Val	Gln	5					10	•				Leu 15		
' 1	Thr	Val	Gln	5					10	•						
l Ser	Thr Leu	Val Ile Leu	Gln Leu 20	5 Asn	Asn	Val	Ala Arg	A1 a 25	10 Phe	Thr	Ser	Asn Leu	Trp 30	15	Cys	
l Ser Gln	Thr Leu Thr Trp	Val Ile Leu 35	Gln Leu 20 Glu	5 Asn Asp	Asn Gly	Val Arg Thr	Ala Arg 40	Ala 25 Arg	10 Phe Ser	Thr Val	Ser Gly Ser	Asn Leu 45	Trp 30 Trp	15 Val	Cys Ser	
Ser Gln Cys	Thr Leu Thr Trp 50	Val Ile Leu 35 Leu	Gln Leu 20 Glu Val	5 Asn Asp Asp	Asn Gly Arg	Val Arg Thr 55	Ala Arg 40 Arg	Ala 25 Arg Gly	10 Phe Ser Gly	Thr Val Pro	Ser Gly Ser 60	Asn Leu 45 Pro	Trp 30 Trp Gly	15 Val Arg	Cys Ser Arg	
Ser Gln Cys Ala 65	Thr Leu Thr Trp 50 Gly	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val	5 Asn Asp Asp	Asn Gly Arg Ala 70	Val Arg Thr 55 His	Ala Arg 40 Arg Asp	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu	Thr Val Pro Ala 75	Ser Gly Ser 60 Leu	Asn Leu 45 Pro Gly	Trp 30 Trp Gly Trp	15 Val Arg Ala Gly	Cys Ser Arg Ser 80	
Ser Gln Cys Ala 65 Glu	Thr Leu Thr Trp 50 Gly Ala	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val Val	5 Asn Asp Asp Asp Phe 85	Asn Gly Arg Ala 70 Gln	Val Arg Thr 55 His Glu	Ala Arg 40 Arg Asp Ser	Ala 25 Arg Gly Cys	10 Phe Ser Gly Glu Gly 90	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys	Trp 30 Trp Gly Trp Leu	15 Val Arg Ala Gly Gln 95	Cys Ser Arg Ser 80 Phe	
Ser Gln Cys Ala 65 Glu	Thr Leu Thr Trp 50 Gly Ala	Val Ile Leu 35 Leu Gln	Gln Leu 20 Glu Val Val Gly Arg	5 Asn Asp Asp Asp Phe 85	Asn Gly Arg Ala 70 Gln	Val Arg Thr 55 His Glu	Ala Arg 40 Arg Asp Ser	Ala 25 Arg Gly Cys Arg	10 Phe Ser Gly Glu Gly 90	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys	Trp 30 Trp Gly Trp Leu Leu	15 Val Arg Ala Gly Gln	Cys Ser Arg Ser 80 Phe	
Ser Gln Cys Ala 65 Glu Asp	Thr Leu Thr Trp 50 Gly Ala Met	Val Ile Leu 35 Leu Gln Ala Met Leu	Gln Leu 20 Glu Val Val Gly Arg 100	5 Asn Asp Asp Asp Phe 85 Ala	Asn Gly Arg Ala 70 Gln Cys	Val Arg Thr 55 His Glu Asn	Ala Arg 40 Arg Asp Ser Leu Gly	Ala 25 Arg Gly Cys Arg Val 105	10 Phe Ser Gly Glu Gly 90 Ala	Thr Val Pro Ala 75 Thr	Ser Gly Ser 60 Leu Val	Asn Leu 45 Pro Gly Lys Ala Pro	Trp 30 Trp Gly Trp Leu Leu 110	15 Val Arg Ala Gly Gln 95	Cys Ser Arg Ser 80 Phe Ala	
Ser Gln Cys Ala 65 Glu Asp	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp	Val Ile Leu 35 Leu Gln Ala Met Leu 115	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe	Asn Gly Arg Ala 70 Gln Cys Leu	Val Arg Thr 55 His Glu Asn Leu	Ala Arg 40 Arg Asp Ser Leu Gly 120	Ala 25 Arg Gly Cys Arg Val 105 Leu	10 Phe Ser Gly Glu Gly 90 Ala	Thr Val Pro Ala 75 Thr Thr	Ser Gly Ser 60 Leu Val Ala Leu Ala	Asn Leu 45 Pro Gly Lys Ala Pro 125	Trp 30 Trp Gly Trp Leu Leu 110 Leu	15 Val Arg Ala Gly Gln 95 Thr	Cys Ser Arg Ser 80 Phe Ala	
Ser Gln Cys Ala 65 Glu Asp Gly Pro	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp 130	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe Cys	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu 135	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu Ala	10 Phe Ser Gly Glu Gly 90 Ala Val Met	Thr Val Pro Ala 75 Thr Thr Gly Ala	Ser Gly Ser 60 Leu Val Ala Leu Ala 140	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala	Trp 30 Trp Gly Trp Leu 110 Leu Phe	15 Val Arg Ala Gly Gln 95 Thr Leu Gln	Cys Ser Arg Ser 80 Phe Ala Ser	
Ser Gln Cys Ala 65 Glu Asp Gly Pro	Thr Leu Thr Trp 50 Gly Ala Met Gln Asp 130	Val Ile Leu 35 Leu Gln Ala Met Leu 115 Ala	Gln Leu 20 Glu Val Val Gly Arg 100 Thr	5 Asn Asp Asp Asp Phe 85 Ala Phe Cys	Asn Gly Arg Ala 70 Gln Cys Leu Trp	Val Arg Thr 55 His Glu Asn Leu Glu 135	Ala Arg 40 Arg Asp Ser Leu Gly 120 Glu	Ala 25 Arg Gly Cys Arg Val 105 Leu Ala	10 Phe Ser Gly Glu Gly 90 Ala Val Met	Thr Val Pro Ala 75 Thr Thr Gly Ala	Ser Gly Ser 60 Leu Val Ala Leu Ala 140	Asn Leu 45 Pro Gly Lys Ala Pro 125 Ala	Trp 30 Trp Gly Trp Leu 110 Leu Phe	15 Val Arg Ala Gly Gln 95 Thr	Cys Ser Arg Ser 80 Phe Ala Ser	

				165					170					175		
Leu	Leu	Ala	Thr 180	Leu		Ala	Ala	Cys 185	Ser		Gly	Thr	Phe 190	175 Ser	Thr	
Arg	Gly	Arg 195		Ala	Trp	Pro	Pro 200									
	<	211> 212>	379 297 DNA Hom		pien	S			•							
	<		CDS (1)	(	297)					-						
	<;	222>	mis (1) n =	(	297)											
	gnc		acg									atc Ile				48
												gtg Val				96
												ccc Pro 45				144
												cct Pro				192
												cat His				240
												ttc Phe				288

297

518

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act ggt tag
Thr Gly *
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      <211> 98
      <212> PRT
      <213> Homo sapiens
      <220>
      <221> VARIANT
      <222> (1)...(98)
      <223> Xaa = Any Amino Acid
      <400> 380
Met Xaa Xaa Thr Leu Val Val Ile Cys Thr Ala Val Ile Val Val Val
Ala Leu Thr Arg Lys Lys Ala Leu Arg Ile His Ser Val Glu Gly Asp
Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
                            40
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
                    70
                                         75
Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe Thr Glu
Thr.Gly
      <210> 381
      <211> 264
      <212> DNA
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      <221> CDS
      <222> (1)...(264)
      <400> 381
atg gct gtc tta gta ctt cgc ctg aca gtt gtc ctg gga ctg ctt gtc
Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
```

10

48

						gca Ala										96
			-			aaa Lys	-				-					144
			-	-		gag Glu 55					_	_				192
			-			agc Ser				-	-		-	_		240
-	gga Gly					aag Lys	tga *									264
	<2 <2	210> 211> 212> 213>	87 PRT	o saț	oi ens	5										*
	<4	400>	382													
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Leu	Phe	Leu	Thr 20	Cys	Tyr	Ala	Asp	Asp 25	Lys	Pro	Asp	Lys	Pro 30	Asp	Asp	
Lys	Pro	Asp 35		Ser	Gly	Lys	Asp 40		Lys	Pro	Asp	Phe 45		Lys	Phe	
Leu		Leu	Leu	Gly	Thr	G1u 55	Ile	Ile	Glu	Asn	Ala 60	Val	Glu	Phe	II.e	
	50			-		33										
65					70	Ser	Thr	Gly	Phe	Met 75		Phe	Asp	Asp	Asn 80	

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<212> DNA

	< <	213>	Home	o sa	pien	S											
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		_	-		cac His	-			_					-			96
					cag Gln												144
					ctg Leu												192
					gaa Glu 70					taa *							225
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1 Thr	Cys	Leu	Ala 20		His	Leu	Leu	G1n 25		Ala	Phe	Glu	His 30	15 Thr	Thr		
Gln		Ala 35		Аlа	Gln	Glu	Val 40		Pro	GIn	Glu	Val 45		Gly	Şer		
	Leu 50	Leu			Leu	55	Ala			Asp	Ser 60		Ser	Gly	Thr		
Val 65	Leu	Pro	Glu	G1n	G1u 70	Thr	Pro	Arg	Glu								

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      <221> CDS
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Met Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa Xaa
                                     10
ntg ctg ctg ctg ctg ctg agt ctg gcg ctg ctg ggc gcc cgg gcc
                                                                       96
Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
             20
                                 25
cgc gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca tgc
                                                                      144
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
         35
                             40
gtg gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac ctg
                                                                      192
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
     50
                         55
                                             60
cgg aag aca gcc tgc agc ctg gac gcg cgg acg gag acc cta ctg ctg
                                                                     240
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
65
                     70
                                         75
cag gca gag cgc cgt gcc ctg tgt gcc tgc tgg cca gcg ggg cac tga
                                                                     288
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His *
                 85
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<211> 95

<212> PRT

<213> Homo sapiens

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	50					55					60					
			ctg Leu													24(
			gca Ala									-				288
			gaa Glu 100													336
			tgg Trp	tga *												351
		211> 212>	388 116 PRT Homo	sap	oiens	5										
Met 1			388 Leu	Arg 5	Ser	Leu	Ala	Ala	Thr 10	Thr	Leu	Ala	Leu	Phe 15	Leu	
Val	Phe	Val	Phe 20	Leu	Gly	Asn	Ser	Ser 25	Cys	Ala	Pro	Gln	Arg 30		Leu	
G1u	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40	Ala	Met	Leu	Tyr	Leu 45	Ļys	Gly	Ala	
Gln	Gly 50	Arg	Arg	Phe	Ile	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser	
Asp 65	Arg	Pro	Leu	Pro	G1u 70	Arg	Arg	Ser	Pro	Asn 75	Pro	Gln	Leu	Leu	Thr 80	
	Pro	Glu	Ala	Ala 85		Пe	Leu	Leu	A1a 90		Leu	Gln	Lys	Ser 95		
	Asp Leu		Glu 100		Asn	Phe	Asp	G1n 105	-	Arg	Phe	Leu	Glu 110		Ser	
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<210> 390

<211> 105

<212> PRT

<213> Homo sapiens

<400> 390

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val

1 Gly	Gly	Ala	Gln	5 Val	Leu	Ala	Thr	Gly	10 Lys	Thr	Pro	Gly	Ala	15 Glu	Ile	
Asp	Phe		20 Tyr	Ala	Leu	Пе		25 Thr	Ala	Val	Gly	Val	30 Ala	Ile	Ser	
Ala		35 Phe	Leu	Ala	Leu		40 Ile	Cys	Met	Ile	Arg	45 Arg	His	Leu	Phe	
Asp 65	50 Asp	Asp	Ser	Ser	Asp 70	55 Leu	Lys	Ser	Thr	Pro 75	60 Gly	Gly	Leu	Ser	Asp 80	
	Ile	Pro	Leu	Lys 85		Arg	Аlа	Pro	Arg 90		Asn	His	Asn	Phe 95		
Lys	Arg	Asp	Ala 100		Val	Ile	Ğlu	Leu 105						,,,		
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ato		100>		620	ata	201	200	000	nac	000	ctg	200	2+4	200	029	40
											Leu	-	_	-	_	48
											gta Val					96
											ctg Leu					144
gcc Ala															•	150

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Gly Pro His Pro Leu Val His Ile Thr Glu Glu Val Glu Glu Asn Arg
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Thr Gln Asp Gly Lys Pro Glu Arg Ile Ala Gln Leu Thr Trp Asn Glu
                            40
Ala
      <210> 393
      <211> 294
      <212> DNA
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      <221> CDS
      <222> (1)...(294)
      <400> 393
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Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu
1
                                                          15
ccc cag gag cag ata cag gcc gag ctg agc ccc gcc cat gac cgt cgc
                                                                       96
Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg
             20
                                 25
cca ctg cca ggt ggg gac gag gcc atc act gcc atc tgg gag acc cgg
                                                                      144
Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg
         35
                             40
                                                  45
cta aag gcc caa ccc tgg ctc ttc gac gcc ccc aag ttc cgc ctg cac
                                                                      192
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Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 70 75 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 85 90 ttc tga 294 Phe *

<210> 394 <211> 97 <212> PRT <213> Homo sapiens

<400> 394

 Met
 Asp
 Pro
 Glu
 Val
 Thr
 Leu
 Leu
 Leu
 Gln
 Cys
 Pro
 Gly
 Gly
 Gly
 Leu

 Pro
 Gln
 Glu
 Gln
 Ala
 Glu
 Leu
 Ser
 Pro
 Ala
 His
 Asp
 Arg
 Arg

 Pro
 Leu
 Pro
 Gly
 Gly
 Asp
 Glu
 Ala
 Ile
 Thr
 Ala
 Ile
 Trp
 Glu
 Thr
 Arg
 Arg
 Arg
 Ala
 Pro
 Leu
 Pro
 Arg
 Arg
 Arg
 Fro
 Ile
 Gly
 Pro
 Arg
 Arg
 Arg
 Fro
 Ile
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<221> CDS

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Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
                       55
                                          60
Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
                                      75
                                                         80
Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met
                                  90 .
Glu Asn Glu Thr
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      <211> 141
      <212> DNA
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      <221> CDS
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      <400> 397
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                5
                                   10
                                                      15
ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg
                                                                   96
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
                               25
gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga
                                                                  141
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu *
        35
                           40
                                               45
     <210> 398
     <211> 46
     <212> PRT
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     <400> 398
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                5
                                  10
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
                              25
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu
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							cct Pro 25						96	
							gcc Ala						144	
							agc Ser		-	-	~	•	192	
							cat His						240	
							999 Gly						288	
							cat His 105						336	
				atg Met	gag G1u	tga *							360	

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Trp Lys His Arg Val Ala Thr Arg Phe Thr Leu Pro Arg Phe Leu Gln

40

	aga Arg 50		-		-								_			192
	atc Ile															240
	tct Ser	-	-													288
	gca Ala					-					-					336
	aac Asn															384
	tct Ser 130		-											-		432 *
	caa Gln	-		-									tag *			474
	<2 <2	210> 211> 212> 213>	157 PRT	sar	oiens											
	</td <td>400&gt;</td> <td>402</td> <td></td>	400>	402													
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Ser	Leu	Leu	Leu 20	Leu	Leu	Val	Val	Cys 25	Gly	Пe	Gly	Cys	Val 30	Trp	His	
Trp	Lys	His 35		Val	Ala	Thr	Arg _. 40	Phe	Thr	Leu	Pro	Arg 45		Leu	Gln	
Arg	Arg 50		Ser	Arg	Arg	Lys 55	. •	Cys	Thr	Lys	Thr 60		Leu	Gly	Pro	

Arg 65	Ile	Ile	Gly	Leu	Arg 70	His	Glu	Ile	Ser	Va1 75	Glu	Thr	Gln	Asp	His 80	
	Ser	Ala	Val	Arg 85		Asn	Asn	Thr	His 90		Asn	Tyr	Glu	Asn 95		
Glu	Ala	Gly	Pro 100	Pro	Lys	Ala	Lys	Gly 105	Lys	Thr	Asp	Lys	Glu 110		Tyr	
Glu	Asn	Thr 115		Gln	Ser	Asn	Phe 120	Glu	Glu	His	Пе	Tyr 125	Gly	Asn	G1u-	
Thr	Ser 130	Ser	Asp	Tyr	Tyr	Asn 135	Phe	Gln	Lys	Pro	Arg 140	Pro	Ser	Glu	Va1	
Pro 145	Gln	Asp	Glu	Asp	Ile 150	Tyr	Ile	Leu	Pro	Asp 155	Ser	Tyr				
	<	210> 211> 212> 213>	279 DNA	o saj	oiens	5										
	<	220> 221> 222>		(2	279)											
	<	400>	403													
											tat Tyr				Val	48
											ggt Gly					96
											gag Glu			-	-	144
											gag Glu 60					192
											cta Leu			-	•	240

96

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn * 85 90

<210> 404

<211> 92

<212> PRT

<213> Homo sapiens

<400> 404

Met Trp Pro Val Phe Trp Thr Val Val Arg Thr Tyr Ala Pro Tyr Val 1 5 10 15

Thr Phe Pro Val Ala Phe Val Val Gly Ala Val Gly Tyr His Leu Glu 20 25 30

Trp Phe Ile Arg Gly Lys Asp Pro Gln Pro Val Glu Glu Glu Lys Ser 35 40 45

Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys 50 55 60

Asp His Thr Gln Val Val Ser Leu Lys Asp Lys Leu Glu Phe Ala Pro 65 70 75 80

Lys Ala Val Leu Asn Arg Asn Arg Pro Glu Lys Asn 85 90

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cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc Gln Pro Lys Arg Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20 25 30

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt
Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser
35 40 45

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gga atg aat toa gtt agc too att cag aac caa atg cag too aag gga
                                                                      192
Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly
     50
                         55
ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat
                                                                     240
Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp
                     70
                                         75
acg aag gcg gga tag
                                                                     255
Thr Lys Ala Gly *
      <210> 406
      <211> 84
      <212> PRT
      <213> Homo sapiens
      <400> 406
Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro
                 5
                                    10
Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro
                               25
Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser
                           40
Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly
                       55
Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp
                   70
                                        75
Thr Lys Ala Gly
     <210> 407
     <211> 249
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     <221> CDS
     <222> (1)...(249)
     <400> 407
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Met 1	Ala	Ser	Ser	Gly 5	Gly	Ala	Gly	Ala	Ala 10	Ala	Ala	Ala	Ala	Ala 15	Ala	
			_	-		,			gac Asp		_					96
							_		gaa Glu		-			-	-	144
									gaa Glu				_			192
			_				-		ctg Leu	_	_	_	-		_	240
aca Thr	agc Ser	tga *														249
		210>														

<212> PRT

<213> Homo sapiens

<400> 408

<210> 409

Thr Ser

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Met Gln Cys Cys Leu Leu Leu Arg Trp Leu Ala Ser Ala Leu Leu Arg
 1
                 5
                                      10
ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                       96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
                                                                       144
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
                             40
                                                  45
ctg agg gtt tga
                                                                      156
Leu Arg Val *
     50
      <210> 410
      <211> 51
      <212> PRT
      <213> Homo sapiens
      <400> 410
Met Gln Cys Cys Leu Leu Leu Arg Trp Leu Ala Ser Ala Leu Leu Arg
                 5
                                    10
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
                                25
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
        35
                            40
Leu Arg Val
    50
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      <211> 420
      <212> DNA
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	<	222>	miso (1) n =	(4	420)											
_	cac	_	act								-	_	-	ttt Phe 15	-	48
	_	-	•				-	_			_			tcc Ser		96
														gat Asp		144
														acc Thr		192
														cct Pro		240
			-											cca Pro 95		288
		-				-						_	-	tat Tyr		336
			-											aac Asn		384
gcg	ttg	cac	atc	cta	aag	ttt	gaa	gag	tct	aaa	taa					420

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Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys *
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                         135
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      <211> 139
      <212> PRT
      <213> Homo sapiens
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      <221> VARIANT
     <222> (1)...(139)
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Thr Leu Ala Gln Ala Glu Glu Gln Gln Pro Tyr Leu Glu Gly Ser Thr
Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr
                            40
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
                                    90
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
            100
                                105
Val Val His Arg Ile Leu Lys Gly Lys Ile Thr Gly Ala Leu Asn Ser
                            120
Ala Leu His Ile Leu Lys Phe Glu Glu Ser Lys
    130
                     . 135
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      <211> 795
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      <222> (1)...(795)
     <400> 413
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					-				gac Asp		-			48
	_		_	_		-			gtt Val		_	_	_	96
									aag Lys					144
									aat Asn					192
						-			gct Ala 75				_	240
	-	-	-		-		-		aga Arg				-	288
		-			-	-		_	ctt Leu				-	336
	_	_	-	_					agc Ser				-	384
	-	-	-		-	-			ttc Phe					432
	_			_	_				ata Ile 155	_	-			480
									gaa Glu					528

tgt Cys										576
agc Ser						_	-		-	624
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 Phe
 Val
 Pro
 Cys
 Gly
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 Ala
 Pro
 Asp
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 Gly
 Asn
 Val
 Gly
 Gly</th

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Ser	Gly	Cys 115		Arg	۷a٦	Ile	Val 120			Ser	Ser	His 125	Ser		Gln	
Arg	Asn 130		Leu	Gln	Leu	Arg 135	Ser	Thr	Pro	Phe	Arg 140	Tyr		Leu	Thr	
Pro 145		Met	Gln	Lys	Ser 150	Val	Gln	Asn	Lys	Ile 155	Lys	Ser	Leu	Asn	Trp 160	
Glu	Glu	Met	Glu	Lys 165	Ser	Arg	Cys	Ile	Pro 170	GTu	Ile	Asp	Asp	Ser 175	Glu	
Phe	Cys	Ile	Arg 180	He	Pro	Gly	Gly	Gly 185	Ile	Thr	Lys	Thr	Leu 190	Tyr	Asp	
	Ser	195					200					205	-			
	G1u 210					215					220			-		
225	Glu				230					235					240	
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Ser	Gly	Leu	Pro 260	Pro	Ala	Leu	Phe									
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	ctc Leu															96
atc Ile	atg Met	aga Arg 35	aga Arg :	tct Ser	cca Pro	cta Leu	gct Ala 40	gtt Val	gct Ala	gga Gly	ttt Phe	cag Gln 45	gat Asp	gga Gly	gga Gly	144

aga ctc aag cag aga gac ctg gtg gcc act aga agc ttg gaa cag ccc 192 Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro 55 60 tca gtt gat agc aag gaa atg agg act cag tga 225 Ser Val Asp Ser Lys Glu Met Arg Thr Gln * 65 70 <210> 416 <211> 74 <212> PRT <213> Homo sapiens <400> 416 Met Gly Lys Leu Phe Trp Ile Ile Gln Met Asp Cys Val Gln Ser Gln 10 Glu Leu Leu Lys Ala Glu Thr Leu Ser Gln Leu Gly Ser Glu Arg Phe 25 Ile Met Arg Arg Ser Pro Leu Ala Val Ala Gly Phe Gln Asp Gly Gly 40 45 Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro Ser Val Asp Ser Lys Glu Met Arg Thr Gln 70 <210> 417 <211> 414 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(414) <400> 417 atg gag tac ata cag cag ttg aag gac ttt act acc gat gac ctg ttg 48 Met Glu Tyr Ile Gln Gln Leu Lys Asp Phe Thr Thr Asp Asp Leu Leu 1 10 cag cta tta atg tca tgt ccc caa gtt gaa tta att cag tgt ctc act 96 Gln Leu Leu Met Ser Cys Pro Gln Val Glu Leu Ile Gln Cys Leu Thr 20 25 30

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					-							att Ile	-			192
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Lys	Glu	Leu 35		G7u	Lys	Gln	Pro 40		Leu	Ser	Phe	Gly 45		Ala	Ile	
Leu	His 50		Phe	Ser	Ala	Asp 55		Lys	Lys	Val	Gly 60	Ile	Lys	Leu	Leu	
Gln		Ile	Asn	Lys	Gly		Пе	Asp	Ala	Val		Ser	Leu	Met	Ile	

65					70					75					80	
Asn	Asp	Ser	Phe	Cys 85	Ser	Пe	Glu	Lys	Trp 90	Gln	Glu	Val	Ala	Asn 95	Ile	
Cys	Ser	Gln	Asn 100	Gly	Phe	Asp	Lys	Leu 105	Ser	Asn	Asp	Пe	Thr 110	Ser	Ile	
Leu	Arg	Ser 115	Gln	Ala	Ala	۷a٦	Thr 120	Glu	Ile.	Ser	Glu	Glu 125	Asp	Asp	Ala	
Val	Asn 130	Leu	Met	Glu	His	Val 135	Phe	Trp								
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		_	cat His 20									-	-			96
	_		ggc Gly			-								-	-	144
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50

55

60

tgg aag ctg cag gat ggc tgc agg ggg ccg tgg acc ctc ctg gcc tga 240 Trp Lys Leu Gln Asp Gly Cys Arg Gly Pro Trp Thr Leu Leu Ala * 65 70 75

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